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Status Report on Planktonic Cyanobacteria (Blue-Green Algae) and Their Toxins

Wright State Univ., Dayton, OH

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Toxic blue-green algae (cyanobacteria) continue to be agents of certain water-based toxicoses. Their presence is now being acknowledged in many of the world's fresh and brackish waters with eutrophication status of meso to hypereutrophic. Dense surface scums called waterblooms will occur for a few days, weeks or months when temperature, nutrient and stratification status of these water bodies is appropriate. It is during these waterblooms that the concentration of toxins exceeds a level such that any animal can ingest an acutely lethal dose of toxic cells or toxins. Laboratory studies, using subacute levels of the main blue-green toxin group, have shown them to be a potent promoter of liver tumors. It is the continued presence of these toxins in water supplies, plus a new understanding of the toxins' structure and function, that has prompted this status report. This report summarizes the present understanding on toxic blue-green algae and their toxins. This information can be used to define directions for research and bring about those areas of concern for public health studies.

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A STATUS REPORT ON PLANKTONIC CYANOBACTERIA (BLUE-GREEN ALGAE) AND THEIR TOXINS

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FOREWORD

Environmental measurements are required to determine the quality of ambient waters and the character of waste effluents. The Environmental Monitoring Systems Laboratory - Cincinnati (EMSL-Cincinnati) conducts research to:

- Develop and evaluate analytical methods to identify and measure the concentration of chemical pollutants in drinking waters, surface waters, groundwaters, wastewaters, sediments, sludges, and solids wastes.
- Investigate methods for the identification and measurement of viruses, bacteria and other microbiological organisms in aqueous samples and to determine the responses of aquatic organisms to water quality.
- Develop and operate a quality assurance program to support the achievement of data quality objectives in measurements of pollutants in drinking waters, surface waters, groundwaters, wastewaters, sediments, and solid wastes.
- Develop methods and models to detect and quantify responses in aquatic and terrestrial organisms exposed to environmental stressors and to correlate the exposure with effects on chemical and biological indicators.

The overall objective of this document is to advise the U.S. Environmental Protection Agency on the current impact of toxic cyanobacteria (blue-green algae) on the water environment. The document focuses specifically on the toxins of these organisms as they relate to the deterioration of surface water quality. Toxic waterblooms are responsible for sporadic, but recurrent episodes of illness and death among wild and domestic animals. Cyanobacterial toxins have also been implicated in human poisoning from certain municipal and recreational water supplies.

Thomas A. Clark, Director
Environmental Monitoring Systems
Laboratory - Cincinnati

ABSTRACT

Toxic blue-green algae (cyanobacteria) continue to be agents of certain water-based toxicoses. Their presence is now being acknowledged in many of the world's fresh and brackish waters with eutrophication status of meso to hypereutrophic. Dense surface scums called waterblooms will occur for a few days, weeks or months when temperature, nutrient and stratification status of these water bodies is appropriate. It is during these waterblooms that the concentration of toxins exceeds a level such that any animal can ingest an acutely lethal dose of toxic cells or toxins. Laboratory studies, using subacute levels of the main blue-green toxin group, have shown them to be a potent promoter of liver tumors. It is the continued presence of these toxins in water supplies, plus a new understanding of the toxins' structure and function, that has prompted this status report. This report summarizes the present understanding on toxic blue-green algae and their toxins. This information can be used to define directions for research and bring about those areas of concern for public health studies.

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INTRODUCTION

While algae responsible for producing toxins are found in the divisions Chrysophyta (class Prymnesiophyceae), Pyrrhophyta (class Dinophyceae or dinoflagellates) and Cyanophyta (cyanobacteria or blue-green algae), the latter causes most of the problems in freshwater environments (Carmichael 1986, 1988, 1992; Carmichael et al. 1990; Gorham and Carmichael 1988; Beasley et al. 1989). The blue-green algae are prokaryotes (without nuclei) having cell walls composed of peptidoglycan and lipopolysaccharide layers. Many people now refer to them as cyanobacteria (Staley et al. 1989). The main toxic cyanobacterial genera include filamentous *Anabaena, Aphanizomenon, Nodularia, Oscillatoria* and unicellular colonial *Microcystis* (Skulberg et al.; in press). More than one species within these genera can be toxic, and all toxic species can form water blooms. Surface water blooms tend to occur on warm summer and autumn days with light wind when water stagnation and sufficient nutrient concentrations, especially nitrogen and phosphorus, are present (Skulberg et al. 1984; Pearl 1987). Nutrient concentrations, which contribute to bloom formation, result from runoff of either fertilizer, livestock or human wastes. Toxic water blooms can be found in many eutrophic to hypereutrophic lakes, ponds and rivers throughout the world (Table 1). They are responsible for sporadic, but recurrent episodes of wild and domestic animal illness and death. They are also implicated in human poisonings from certain municipal and recreational water supplies.

The primary types of toxicosis include acute hepatotoxicosis, peracute neurotoxicosis, gastrointestinal disturbances, respiratory and allergic reactions. It is not known whether the latter toxicoses are caused by the hepato- or neurotoxic agents or by other chemical groups. It has been suggested, but so far unproven, that lipopolysaccharide (LPS) endotoxins are involved with the gastrointestinal disturbances (Sykora and Keleti, 1981; Martin et al. 1989).

Many cyanobacterial blooms are apparently not hazardous to animals. This can be due to: low or no measurable concentrations of toxin within strains and species comprising the waterbloom; low biomass concentration of the waterbloom; variation in animal species' sensitivity; amount consumed by the animal as well as age, sex and amount of other food in the animal's gut. Since toxic and nontoxic blooms of the same species can be found, it is not always possible to attribute clinical responses to the presence of a bloom of a toxigenic species. Appropriate diagnostic procedures are therefore needed. These include: 1) establish that animals have been drinking from a concentrated surface bloom, 2) microscopic identification of a toxigenic species, or at least genus, as the predominant phytoplankton present, 3) laboratory analysis for the presence of the toxins in the cells, and 4) verification of toxic responses (clinical signs, survival times) in laboratory test animals (intraperitoneal and oral dosed) to verify that the clinical responses are compatible with the properties of the algal toxins detected (Carmichael and Schwartz 1984; Beasley et al. 1989).

Table 1. Known occurrences[1] of toxic cyanobacteria in fresh or marine water. (updated from Gorham and Carmichael, 1988)

- ARGENTINA
- AUSTRALIA
- CHILE
- BANGLADESH
- BERMUDA
- BRAZIL

- CANADA
  - Alberta
  - British Columbia
  - Manitoba
  - Ontario
  - Saskatchewan

- EUROPE
  - Czechoslovakia
  - Denmark
  - Finland
  - France
  - Germany
  - Greece
  - Hungary
  - Italy
  - Netherlands
  - Norway
  - Poland
  - Portugal
  - Russia
  - Sweden
  - Ukraine
  - United Kingdom

- INDIA
- ISRAEL
- JAPAN
- NEW ZEALAND
- OKINAWA (marine only)
- PEOPLES REPUBLIC OF CHINA
- SOUTH AFRICA
- THAILAND

- U.S.A.
  - California
  - Colorado
  - Florida
  - Hawaii (marine only)
  - Idaho
  - Illinois
  - Indiana
  - Iowa
  - Michigan
  - Minnesota
  - Mississippi
  - Montana
  - Nebraska
  - Nevada
  - New Hampshire
  - New Mexico
  - New York
  - North Dakota
  - Ohio
  - Oklahoma
  - Oregon
  - Pennsylvania
  - South Dakota
  - Texas
  - Washington
  - Wisconsin
  - Wyoming

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[1] Based upon reports cited in Tables 4 and 5. Occurrences not listed in Tables 4 and 5 are from previous review articles cited in this report and as primary references cited in the Appendix [The Directory to Toxic Blue-Green Algae (Cyanobacteria) Literature].

CYANOBACTERIA AND THEIR TOXINS

Cyanobacteria (blue-green algae) toxins constitute the major source of natural product toxins "biotoxins" found in surface supplies of freshwater. Species and strains in all of the common planktonic cyanobacterial genera including *Anabaena, Aphanizomenon, Microcystis, Nodularia, Nostoc* and *Oscillatoria* produce biotoxins. Other genera including *Coelosphaerium, Cylindrospermopsis, Fischerella, Gloeotrichia, Gomphosphaeria, Hapalosiphon, Microcoleus, Schizothrix, Scytonema, Spirulina, Symploca, Tolypothrix,* and *Trichodesmium* have been reported toxic, but no toxin has been isolated and characterized as yet from these genera (Scott 1991; Skulberg et al. in press).

These cyanotoxins produce intermittent but repeated cases of animal poisonings in many areas of the world. Poisoning cases, known since the late 19th century, involve sickness and death of livestock, pets and wildlife following ingestion of water containing toxic algae cells or the toxin(s) released by the aging cells (Carmichael and Schwartz 1984; Beasley et al. 1989). No acute lethal poisoning of humans by freshwater cyanobacteria, such as occurs with paralytic shellfish poisoning, has been confirmed. Humans are probably just as susceptible as other mammals but people are repelled by the idea of consuming water containing an algae bloom (Gorham and Carmichael 1988; Falconer 1989, 1991; Carmichael and Falconer in press). Furthermore, there are no known food vectors, such as shellfish, to concentrate toxins of freshwater cyanobacteria in the human food chain. However, the decreasing water quality and increasing eutrophication of our freshwater supplies mean that large growths or waterblooms of cyanobacteria are becoming more common. When tested, these waterblooms are positive for the two main groups of cyanotoxins---the biotoxic alkaloid neurotoxins and the cyclic peptide hepatotoxins.

Survey reports over the last few years indicate that a significant number of blooms are toxic in any given area. In the U.S. many states have reported blooms of toxic cyanobacteria. The only systematic survey study done to date in the U.S. is from Wisconsin. That study reported about 40% of all cyanobacteria blooms tested were toxic during the summer of 1987 (Repavich et al. 1990). Reports from Scandinavia (Sivonen et al. 1990a) and other areas of Europe (Skulberg et al. 1984; Pearson 1990) report a similar percentage pattern. In some cases with small sample numbers, the percentage pattern of toxic blooms has been much higher (Carmichael et al. 1988; Lanaras et al. 1989). Since waterblooms of cyanobacteria commonly result from eutrophication processes, the toxic waterblooms will likely increase in size and duration. It is possible that humans could become exposed to levels of the toxins that can cause acute toxicity.

Neurotoxins

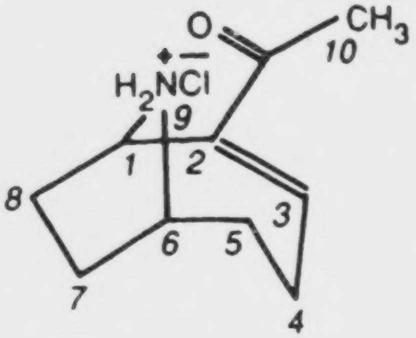
Neurotoxins are produced by species and strains of *Anabaena* (Carmichael et al. 1990), *Aphanizomenon* (Mahmood and Carmichael 1986a), *Oscillatoria* (Sivonen et al. 1989a; Skulberg et al. 1992) and *Trichodesmium* (Hawser et al. 1991). Five chemically defined

neurotoxins are now known from species within these genera. Anatoxin-a (antx-a
first toxin from a freshwater cyanobacterium to be chemically and functionally d
is the secondary amine, 2-acetyl-9-azabicyclo[4.2.1]non-2-ene (Huber 1972; De
1977), molecular weight 165 (M/Z) daltons (Figure 1). It has been synthesized by
of different methods (summarized in Carmichael et al. 1990). This alkaloid neu
a potent postsynaptic cholinergic nicotinic agonist, which causes a de
neuromuscular blockade (Carmichael et al. 1975, 1979; Spivak et al. 1980, 1983;
and Witkop 1981). Signs of toxicosis in field cases for wild and domestic anima
staggering, muscle fasciculation, gasping, convulsions, and opistothonos (birds).
probably due to respiratory arrest and occurs within minutes to a few hours depe
species, dosage, and prior food consumption. The LD_{50} intraperitoneal (i.p.) m
purified toxin is about 200 g/kg body weight, with a survival time of minutes. Whil
dose to produce acute lethality is much higher (hundreds of mg/kg body weight fo
weight cell material), the toxicity is still high enough that animals need to ingest o
milliliters to a few liters of the toxic surface waterbloom to receive a leth
(Carmichael and Gorham 1977; Carmichael et al. 1977; Carmichael and Biggs 19

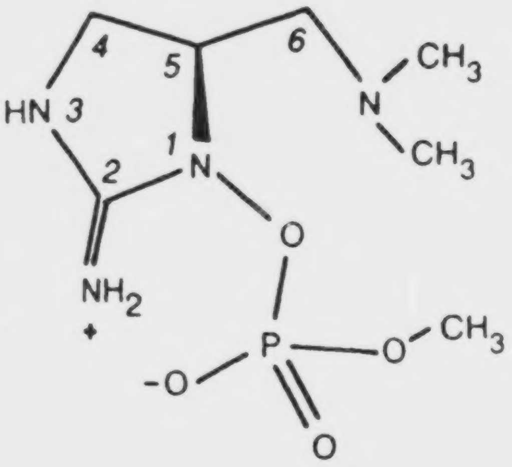
No chemical antidote exists for antx-a intoxication. Artificial respiration has b
in one instance with only partial success (Carmichael et al. 1977). However, Beas
(1989) report a dose dependent reversal of antx-a toxicosis in laboratory rats using
respiration. They suggest that animals given prolonged artificial respiration in ad
lavage and instillation of activated charcoal should recover. Detection of antx-
primarily by the mouse bioassay. There are some analytical methods, which deve
methods of purification, were being used. These are based upon high performan
chromatography (HPLC) (Astrachan and Archer 1981; Wong and Hindin 1982; H
al. 1989), thin layer chromatography (Ojanpera 1991), gas chromatogra
spectrometry (GC-MS) (Smith and Lewis 1987; Himberg 1989), and gas chromat
electron capture detection (GC-ECD) (Stevens and Krieger 1988).

Most reports of antx-a occurrence are associated with *Anabaena flos-aquae, A.*
or *A. circinalis*. Recently *Oscillatoria* has been shown to produce antx-a (Sivone
1989a) and a strain of *Oscillatoria rubescens* has been shown to produce a me
homologue of antx-a termed homoanatoxin-a (Skulberg et al. 1992; Figure 2)
homologue has a similar toxicity as antx-a.

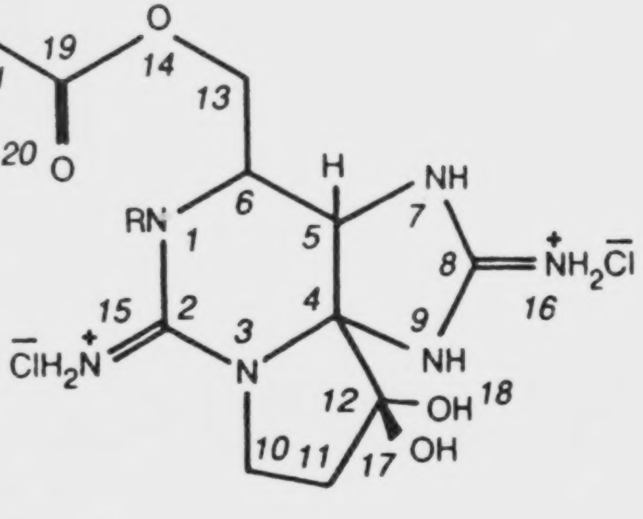
Anatoxin-a is not the only neurotoxin to be produced by species and st
Anabaena. During screening of different *Anabaena* field samples Carmichael and
(1978) noted that some samples produced different signs of neurotoxicosis. In pa
some samples produced a marked salivation in laboratory mice. In order to diffe
this from signs observed with antx-a the toxin was designated as anatoxin-a(s) [s=sali
Antx-a(s) was subsequently shown to be a potent inhibitor of cholinesterase (Mahm
Carmichael 1986b, 1987). Structurally antx-a(s) is a unique N-hydroxyguanidine
phosphate ester (m/z 252; $C_7H_{17}N_4O_4P$) (Matsunaga et al. 1989) (Figure 1). To dat
is no evidence which would indicate that strains of *Anabaena* produce both anatoxi


O
CH3
10
H2NCl
9
1
2
3
4
5
6
7
8

anatoxin - a hydrochloride
(m/z 165)
$C_{10}H_{15}NO$


4
5
6
CH3
N
CH3
HN 3
1
N
2
O
NH2
+
P
O
CH3
-O
O

anatoxin - a(s)
(m/z 252)
$C_7H_{17}N_4O_4P$


H2N
19
O
14
21
13
20 O
RN
1
6
5
H
NH
7
8
NH2Cl
16
15
2
4
9
ClH2N
3
N
NH
12
OH 18
10 11
17 OH

R = H; saxitoxin dihydrochloride
R = OH; neosaxitoxin dihydrochloride

Figure 1. Structure of anatoxin-a produced by species and/or strains of *Anabaena flos-aquae, Aphanizomenon flos-aquae* and *Oscillatoria* sp.; anatoxin-a(s) produced by *Anabaena flos-aquae*; and saxitoxin, neosaxitoxin produced by *Aphanizomenon flos-aquae* and certain marine microorganisms.

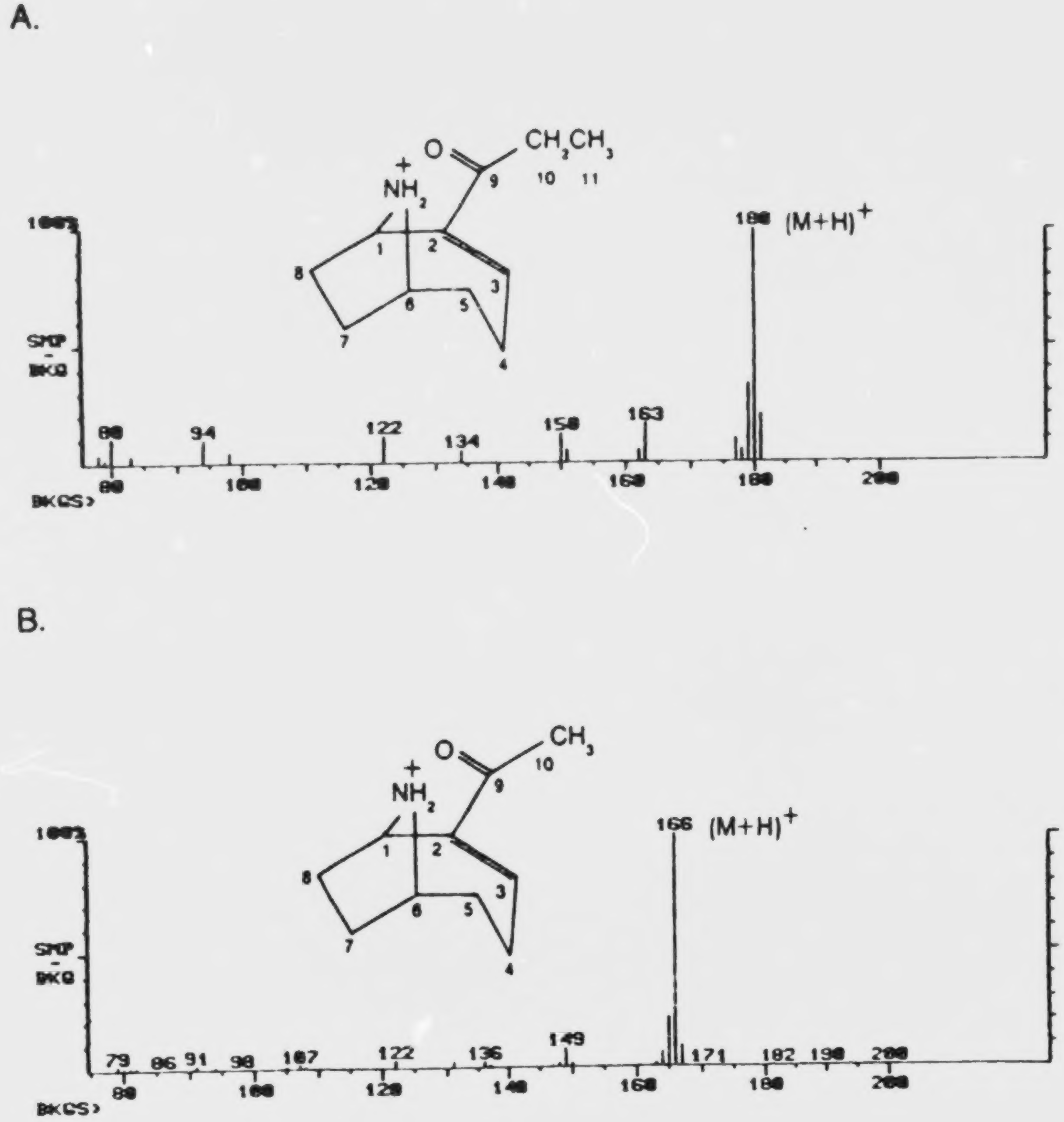


Figure 2. FAB-MS of methylene (homo) anatoxin-a (A) produced by *Oscillatoria* (Skulberg et al. 1992) and anatoxin-a (B).

a(s). Toxicosis associated with cholinesterase-inhibiting algae have been reported in dogs and calves in South Dakota (Mahmood et al. 1988) and in pigs and ducks in Illinois (Cook et al. 1989).

Clinical signs of toxicosis from laboratory experiments involving dosing of antx-a(s) have been observed in ducks and pigs (Beasley et al. 1989). The LD_{50} i.p. mouse for Antx-a(s) is about 20 g/kg body weight or about ten times more lethally toxic than antx-a. At the LD_{50} the survival time for mice is 10-30 minutes. Since antx-a(s) has the properties of an organophosphorus insecticide, it should be possible to use therapy such as atropine to antagonize its toxicosis. This has been partially successful (Mahmood and Carmichael 1986b; Beasley et al. 1989), but further studies are needed.

Kinetic studies comparing antx-a(s) with the organophosphate (OP) diisopropylfluorophosphate (DFP) and studies looking at the nature of the interaction of antx-a(s) and acetylcholinesterase have shown that antx-a(s) is an irreversible inhibitor of cholinesterase. Comparing the bimolecular inhibition constants between antx-a(s) and the very potent synthetic OP DFP, showed that antx-a(s) is about 22 times more potent than DFP (Carmichael et al. 1990). This work plus that of Hyde and Carmichael (1991) suggests that antx-a(s) uses the two-site attachment mechanism analogous to substrate and does not inhibit acetylcholinesterase in the manner of the reversible anticholinesterases (Figures 3-4).

Aphanizomenon flos-aquae producing neurotoxins was first demonstrated by Sawyer et al. (1968). These neurotoxins were later shown to be saxitoxin (STX) and neosaxitoxin (NEOSTX) (LD_{50} i.p. mouse equals about 10 g/kg), the two primary toxins of red tide paralytic shellfish poisoning (PSP) (Sasner et al. 1984; Mahmood and Carmichael 1986a). Most work on STX and NEOSTX has been done using strains NH-1 and NH-5 isolated by Carmichael in 1980 from a small pond near Durham, New Hampshire (Carmichael 1982; Ikawa et al. 1982). These toxins are fast acting neurotoxins that inhibit nerve conduction by blocking sodium channels without affecting permeability to potassium, the transmembrane resting potential, or membrane resistance (Adelman et al. 1982). Mahmood and Carmichael (1986a), using the NH-5 strain, showed that batch cultured cells have a mouse i.p. LD_{50} of about 5 mg/kg. Each gram of lyophilized cells yielded about 1.3 mg of neosaxitoxin and 0.1 mg of saxitoxin (Figure 1c). Shimizu et al. (1984) studied the biosynthesis of the STX analog NEOSTX using *Aph. flos-aquae* NH-1. More recently Sivonen et al. (1989a) has demonstrated antx-a production in a strain of *Aph. flos-aquae.*

Hepatotoxins

Acute hepatotoxicosis involving the hepatotoxins (liver toxins) is the most commonly encountered toxicosis involving cyanobacteria. These toxins are produced by strains of species within the genera *Microcystis, Anabaena, Nodularia, Oscillatoria* and *Nostoc.* In addition, chemically undefined hepatotoxins are being studied in *Cylindrospermopsis, Aphanizomenon, Gloeotrichia,* and *Coelosphaerium.* Clinical signs of hepatotoxicosis have been observed in field poisonings involving cattle, sheep, horses, pigs, ducks, and other wild

Hydrolysis of Substrate by AChE

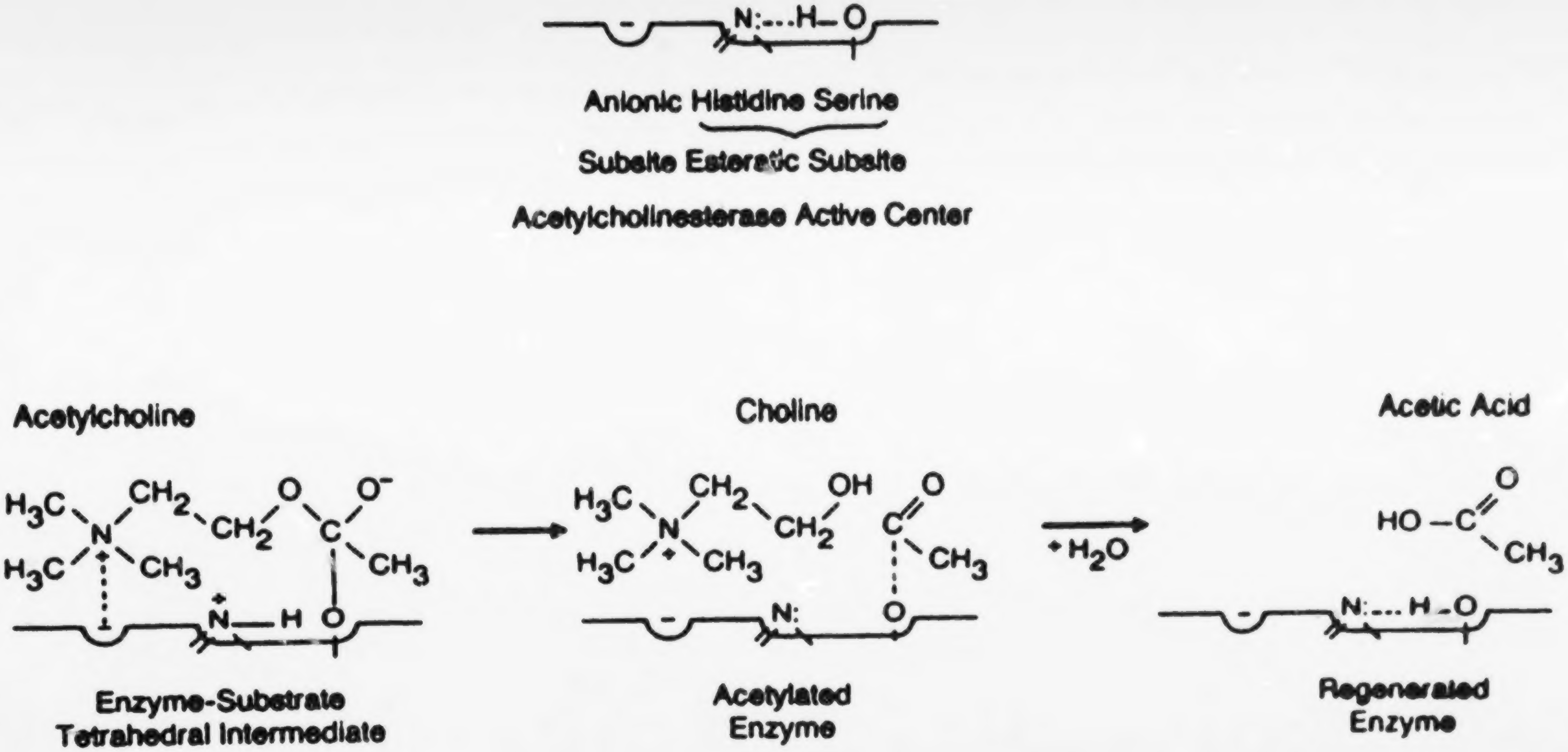

N:---H–O
Anionic Histidine Serine
Subsite Esteratic Subsite
Acetylcholinesterase Active Center
Acetylcholine
Choline
Acetic Acid
H3C
CH2
CH2
O
O⁻
C
CH3
N
+
H
OH
HO
+H2O
Enzyme-Substrate
Tetrahedral Intermediate
Acetylated
Enzyme
Regenerated
Enzyme

Figure 3. Hydrolysis of the substrate acetylcholine by acetylcholinesterase (AChE) in the normal condition at nerve-muscle synapses.

Hydrolysis of Anatoxin-a(s) by AChE

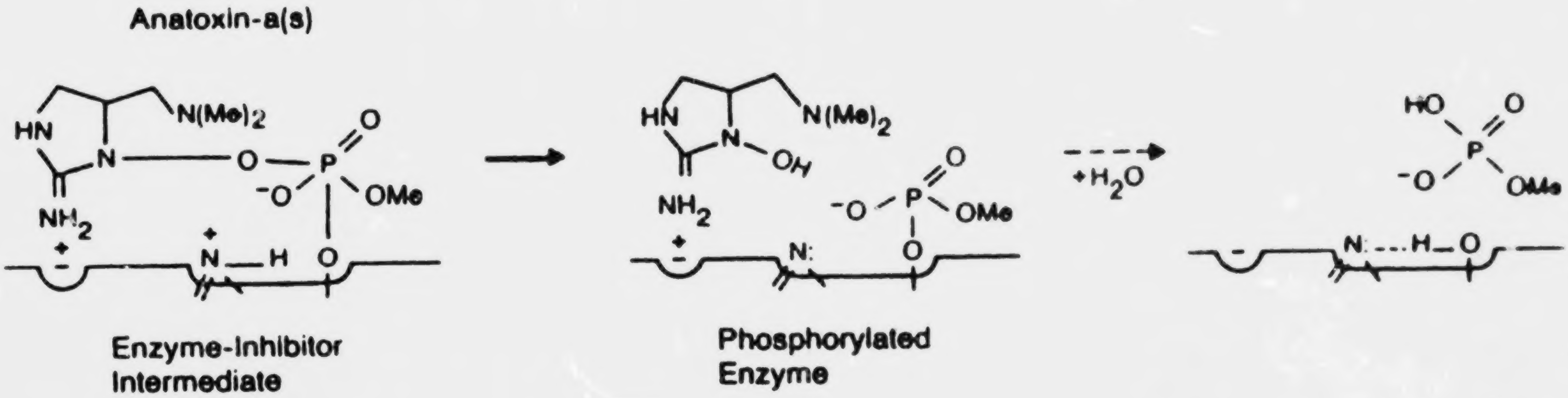

Anatoxin-a(s)
HN
N(Me)2
N
O
P
O
-O
OMe
NH2
+
-
+
N
H
O
Enzyme-Inhibitor Intermediate
HN
N(Me)2
N
OH
NH2
+
-
-O
P
O
OMe
O
N:
Phosphorylated Enzyme
+H2O
HO
O
P
-O
OMe
-
N:
H
O

Figure 4. A possible scheme for hydrolysis of anatoxin-a(s). Note dotted arrow indicates slow dephosphorylation of the enzyme leading to prolonged (irreversible) inhibition of AChE by anatoxin-a(s).

and domestic animals. Most laboratory studies have involved the use of mice, rats, guinea pigs, rabbits and pigs. Collectively, the signs of poisoning in these animals include weakness, anorexia, pallor of mucous membranes, vomiting, cold extremities, and diarrhea. Death occurs within a few hours to a few days after initial exposure and may be preceded by coma, muscle tremors and forced expiration of air (Carmichael and Schwartz 1984; Beasley et al. 1989). Death most likely results from intrahepatic hemorrhage and hypovolemic shock (Berg and Soli 1985 a,b; Theiss et al. 1988). This conclusion is based on increases in liver weight as a fraction of body weight (up to 100% in small animals tested in the laboratory) as well as in hepatic hemoglobin and iron concentrations that account for blood loss sufficient to induce irreversible shock. In animals that live longer, i.e., a few days, hepatic insufficiency may develop to a degree that becomes incompatible with life (Jackson et al. 1984).

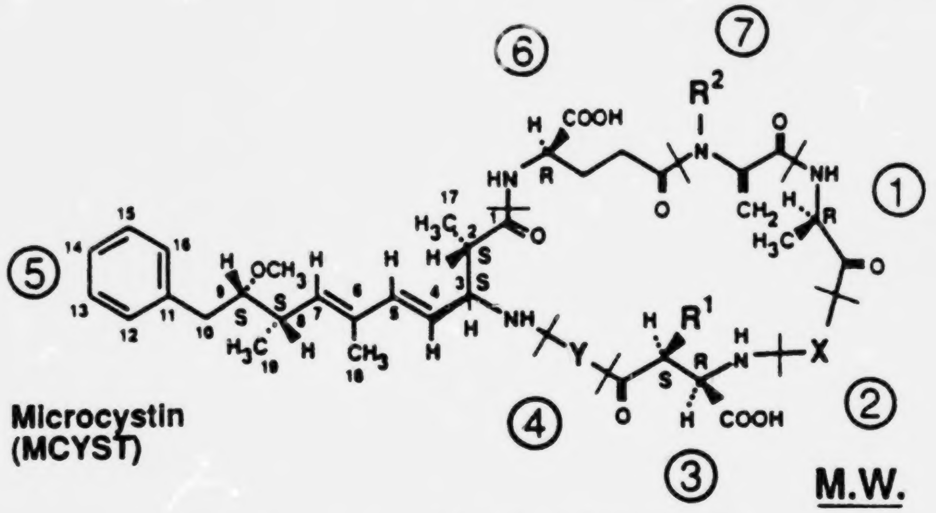
The mechanism of action for these hepatotoxins is the subject of current research in several laboratories. Putting together certain aspects of this research it is possible to sketch a sequence of events that could explain the hemorrhagic shock (based on a summary described by Beasley et al. 1989). First, the toxin(s) are absorbed into the blood from the ileum. Uptake in this area of the intestine may reflect the activity of abundant bile acid carriers as conveyers of the peptide toxins across the mucosa (Dahlem et al. 1988). Second, there is evidence that the toxin is transported preferentially into the hepatocytes (Runnegar et al. 1981; Dabholkar and Carmichael 1987; Meriluoto et al. 1990). The mechanism of uptake into hepatocytes is believed to be via bile acid carrier salt transport (Runnegar et al. 1981; Eriksson et al. 1990). This transport mechanism has not been proven but evidence is clear that the uptake is at least carrier mediated (Runnegar et al. 1991). Third, hepatotoxin induced changes in the actin microfilaments, composing part of the cells cytoskeleton, leads to a dense aggregation of the microfilaments near the center of the cell (Runnegar and Falconer 1986; Eriksson et al. 1989; Hooser et al. 1991). As a result of these cytoskeletal changes there is a loss of cell-cell adhesion and the hepatocytes separate leading to destruction of the sinusoid endothelial cells. Without intact liver sinusoids, lethal intrahepatic hemorrhage (within hours) and/or hepatic insufficiency occurs within days. Recent research is being directed toward the biochemical events leading to the microfilament effects---these will be summarized once the structure of these hepatotoxins has been presented.

Microcystins

The first report of these hepatotoxins being peptides was from *Microcystis aeruginosa* strain NRC-1 (ss-17) by Bishop et al. (1959). This toxin was later named microcystin (MCYST) by Konst et al. (1965) and Carmichael et al. (1988b). Subsequent isolations of MCYST were made from the same strain (Murthy and Capindale 1970; Rabin and Darbre 1975) and from *M. aeruginosa* blooms in South Africa (Torrien, Scott and Pitout 1976) and Australia (Elleman et al. 1978; Runnegar and Falconer 1981). Although the various extracts had similar toxic properties, the hydrolysates of partially pure MCYST had substantially different amino acid compositions which was later concluded to be due to the presence of different microcystins and to the varying degree of purity for the various extracts. Eloff, Siegelman and Kycia (1982) were able to show that a single strain was capable of producing more than one toxin, but it remained for Botes and his colleagues (Botes, Kruger and Viljoen 1982; Botes et al. 1982a,b) and Santikarn et al. (1983) to provide us with the structure of one of these toxins (designated as Microcystis toxin BE-4) produced by the South African *Microcystis aeruginosa* strain WR70 (= UV-010). They concluded the toxin to be a monocyclic peptide containing both D and L amino acids. Two of the D amino acids were the novel N-methyldehydroalanine (Mdha) (which gives methylamine upon hydrolysis) and a nonpolar side chain blocking group of 20 carbon atoms with a mass of 313 daltons termed ADDA (3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid). The two L amino acids were found to differ between the various toxins, and for the BE-4 toxin the L amino acids were leucine and alanine. Later Botes et al. (1985) reported the structure of four other related toxins having L amino acid combinations of -LR (leucine-arginine); -YR (tyrosine-arginine); -YA (tyrosine-alanine); and -YM (tyrosine-methionine).

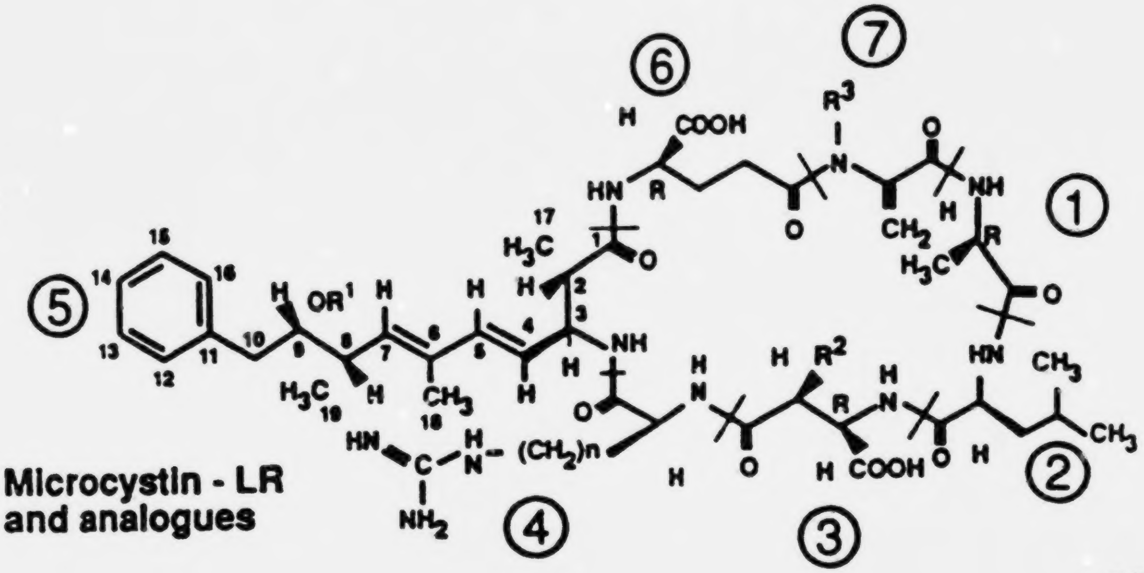
The South African work was followed by Krishnamurthy et al. (1986, 1989) who found the -LR toxin in a Norwegian waterbloom of *M. aeruginosa* and a Canadian *Anabaena flos-aquae*. They also found the -RR (arginine-arginine) toxin in a Norwegian laboratory culture of *Oscillatoria* (Figures 5-6). The first definitive structure for MCYST-LR was by Rinehart et al. (1988). This was followed by the work of Namikoshi et al. (1989) who published results on the chemical synthesis of the ADDA component of microcystin. ADDA has been shown to be the key structural component for biological activity. Ozonalysis of the double bonds on ADDA yields free ADDA plus the corresponding cyclic peptide minus ADDA. Mouse bioassay of these two structures shows that neither has toxicity in the mouse bioassay (Dahlem 1989). Further structure/function work supports the importance of ADDA as the key functional part of these cyclic peptides. During purification of microcystins using HPLC, a small peak is often observed eluting close to the main toxin peak. When analyzed by Harada et al. (1990a,b) this small peak was found to be a geometrical isomer of the parent toxin. The isomerization was located at the C-8 position of ADDA. The toxins associated with these minor peaks were MCYST-LR and RR. This isomer was found to be nontoxic up to 1 mg/kg i.p. in the mouse bioassay.

Based on these beginnings our structural understanding for these microcystins has progressed to the point where there are now about 23 known cyclic heptapeptide microcystins plus nontoxic epimers of MCYST-LR and RR (Figures 5-7). These microcystins differ in their L amino acid combinations, with MCYST-LR being most common, and in being with or without methyl groups on amino acids 3, 5 and 7. These microcystins' toxicities do not vary greatly. All of the microcystins, except MCYST-RR and the demethylated toxins D-Asp and Dha which have an LD_{50} i.p. mouse of 200-250 µg/kg, have an LD_{50} i.p. mouse of about 60-70 g/kg with similar signs of poisoning. Some biosynthesis work on MCYST-LR is now underway using *M. aeruginosa* strain PCC-7820. These studies using C-13 precursors indicate that the carbon skeleton of ADDA arises from condensation of phenylacetate with four acetates and C-1 methylation of the polyketide chain on C-2, C-6, and C-8. The work also shows that the Masp unit (Figure 6; amino acid


⑥
⑦
R^2
H
COOH
N
O
NH
HN
R
①
17
H_3C
2
1
O
CH_2
H
R
H_3C
15
14
⑤
16
H
OCH_3
H
H
H
S
3
S
O
13
12
11
10
9
S
8
7
6
5
4
S
NH
H
R^1
H
H_3C
H
CH_3
H
H
R
N
X
19
18
S
Y
O
H
COOH
④
②
③
Microcystin
(MCYST)

			M.W.
	MCYST - LA:	X = Leu; R^1 = CH_3; Y = Ala; R^2 = CH_3	909
	MCYST - M(O)R:	X = Met(O); R^1 = CH_3; Y = Arg; R^2 = CH_3	1028
	MCYST - YA:	X = Tyr; R^1 = CH_3; Y = Ala; R^2 = CH_3	959
	MCYST - LR:	X = Leu; R^1 = CH_3; Y = Arg; R^2 = CH_3	994
	MCYST - FR:	X = Phe; R^1 = CH_3; Y = Arg; R^2 = CH_3	1028
	MCYST - AR:	X = Ala; R^1 = CH_3; Y = Arg; R^2 = CH_3	952
	MCYST - YM:	X = Tyr; R^1 = CH_3; Y = Met; R^2 = CH_3	1018
	MCYST - RR:	X = Arg; R^1 = CH_3; Y = Arg; R^2 = CH_3	1037
[D-Asp^3]	MCYST - RR:	X = Arg; R^1 = H; Y = Arg; R^2 = CH_3	1023
[D-Asp^3,Dha^7]	MCYST - RR:	X = Arg; R^1 = H; Y = Arg; R^2 = H	1009
	MCYST - YR:	X = Tyr; R^1 = CH_3; Y = Arg; R^2 = CH_3	1044
	MCYST - HtyrR:	X = Htyr; R^1 = CH_3; Y = Arg; R^2 = CH_3	1055
[D-Asp^3]	MCYST - HtyrR:	X = Htyr; R^1 = H; Y = Arg; R^2 = CH_3	1044
	MCYST - WR:	X = Trp; R^1 = CH_3; Y = Arg; R^2 = CH_3	1067

Figure 5. Structures of known microcystins excluding analogues of MCYST-LR. MCYST-FR (phenylalanine-arginine); AR (alanine-arginine); M(O)R (methionine sulfoxide-arginine) and WR (tryptophan-arginine) are new toxins from *Microcystis* isolated by Namikoshi et al. (1992).

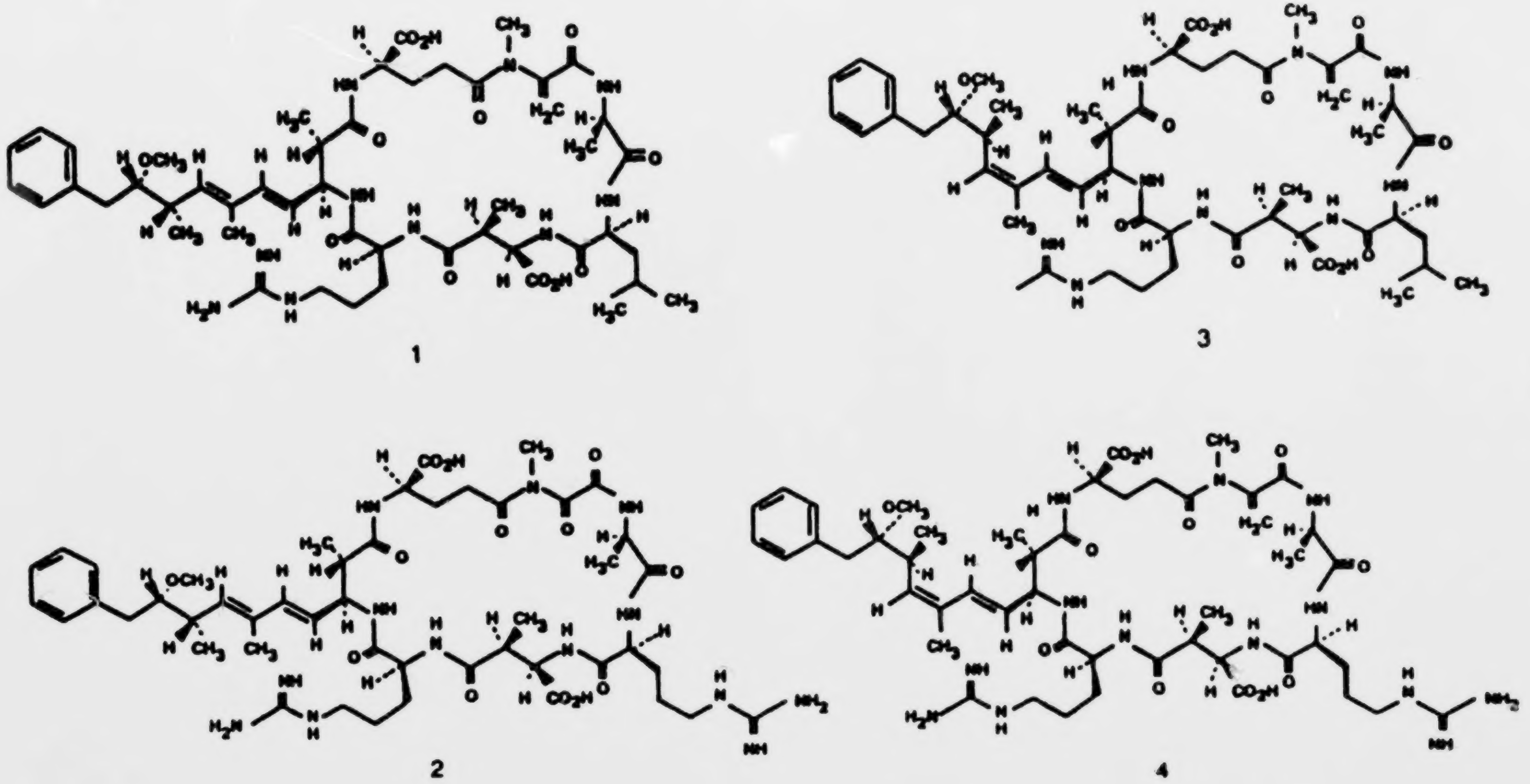


⑦
⑥
H
COOH
R^3
N
O
HN
R
NH
①
O
CH_2
H
R
17
H_3C
1
O
H_3C
15
14
16
H
OR^1
H
H
2
O
⑤
3
13
10
9
8
7
6
5
4
NH
HN
CH_3
11
H
H
R^2
H
12
H
N
R
N
H_3C
H
CH_3
H
H
O
19
18
CH_3
HN
C
H
N
$(CH_2)n$
H
O
H
COOH
O
H
②
NH_2
④
③

Microcystin - LR and analogues

	M.W.
MCYST - LR:$R^1 = CH_3$; = $R^2 = CH_3$; $R^3 = CH_3$; n = 3	994
[ADMAdda^5] - MCYST - LR:$R^1 = \overset{20}{C}O\overset{21}{C}H_3$; $R^2 = CH_3$; $R^3 = CH_3$; n = 3	1022
[ADMAdda^5] - MCYST - LHarg: $R^1 = COCH_3$; $R^2 = CH_3$; $R^3 = CH_3$; n = 4	1036
[D-Asp^3, ADMAdda^5] - MCYST - LR:$R^1 = COCH_3$; = $R^2 = H$; $R^3 = CH_3$; n = 3	1008
[D-Asp^3, ADMAdda^5] - MCYST - LHarg: $R^1 = COCH_3$; $R^2 = H$; $R^3 = CH_3$; n = 4	1022
[D-Asp^3] - MCYST - LR:$R^1 = CH_3$; $R^2 = H$; $R^3 = CH_3$; n = 4	980
[DMAdda^5] - MCYST - LR: $R^1 = H$; $R^2 = CH_3$; $R^3 = CH_3$; n = 3	980
[Dha^7] - MCYST - LR: $R^1 = CH_3$; $R^2 = CH_3$; $R^3 = H$; n = 3	980
[Mser^7] - MCYST - LR: $R^1 = CH_3$; $R^2 = CH_3$; 7 = N - methylserine; n = 3	1012

Figure 6. Structure of microcystin-LR and its analogues. The last three toxins on this list represent new toxins isolated from *Microcystis* by Namikoshi et al. (1992).



Structure of (1) Microcystin - LR; (2) Microcystin - RR; (3) nontoxic minor component of Microcystin - LR; (4) nontoxic minor component of Microcystin - RR.

Figure 7. Structure of microcystin-LR and RR plus nontoxic geometrical isomer minor peaks isolated from *Microcystis* (Harada et al. 1990a,b).

number 3) is formed from acetate and pyruvate via a pathway similar to the biosynthesis of leucine (Moore et al. 1991).

Nodularin

The biggest structure variation for these peptide hepatotoxins has been found in the filamentous brackish water cyanobacterium *Nodularia spumigena*. Earlier reports indicated that *Nodularia* could produce a hepatotoxin (Francis 1878; Main et al. 1977; Lindstrom 1976; Edler et al. 1985; Perrson et al. 1984; Eriksson et al. 1988; Runnegar et al. 1988). Carmichael et al. (1988c), Rinehart et al. (1988), and Sivonen et al. (1989b) established the structure for the *Nodularia* peptide as a cyclic pentapeptide M/Z 824 daltons and termed it nodularin (NODLN) (Figure 8). The sources and types of cyclic peptide toxins produced by the various cyanobacteria are listed in Figure 9.

Occurrence of Toxic Cyanobacteria

Since the first report of toxic cyanobacteria in the late 19th century (Francis 1878) studies in several countries have revealed the wide occurrence of toxic cyanobacteria waterblooms. All continents except Antarctica have reported toxic blooms. In the United States 27 States have reported the presence of toxic cyanobacteria waterblooms, and many of these have documented animal losses (Table 1). In Europe 16 countries have reported toxic cyanobacteria blooms. Although not all of these countries have documented cases of animal, fish or bird poisonings from the waterblooms, the positive laboratory toxicity tests done on waterbloom samples clearly show that the incidence of toxic cyanobacteria is much wider than would be inferred from suspected poisoning incidents. In addition, many of the early toxicosis caused by cyanobacteria waterblooms are difficult to place into any category, since specific toxic signs were not described at that time. It is also possible that other types of toxins were produced in these cases from the cyanobacteria present or the coexisting phytoplankton and bacteria. At present, in all toxicosis cases associated with freshwater phytoplankton, cyanobacteria have been the toxic agent involved. It should be emphasized that toxin forming cyanobacteria are all naturally occurring members of freshwater phytoplankton. The secondary metabolites they produce that are biotoxic can be compared with other natural product toxins. All these natural toxins show a range of toxicities depending on the toxin's potency, the test animal used and the experimental conditions. All the known cyanobacteria toxins are rated as supertoxic when compared against the standard rating table of toxic substances (Table 2). When compared against other biotoxins the cyanotoxins rank more toxic than plant, fungal or some marine phycotoxins toxins and somewhat less toxic than most bacterial and some other marine phycotoxins (Table 3).

The numerous cases of animal poisonings that have been reported in the literature have been summarized at various times over the years (Schwimmer and Schwimmer 1964, 1967; Carmichael et al. 1985; Sivonen 1990). An updated version of these summaries is given in Table 4. A summary of cases the author has investigated over the past 14 years is given in

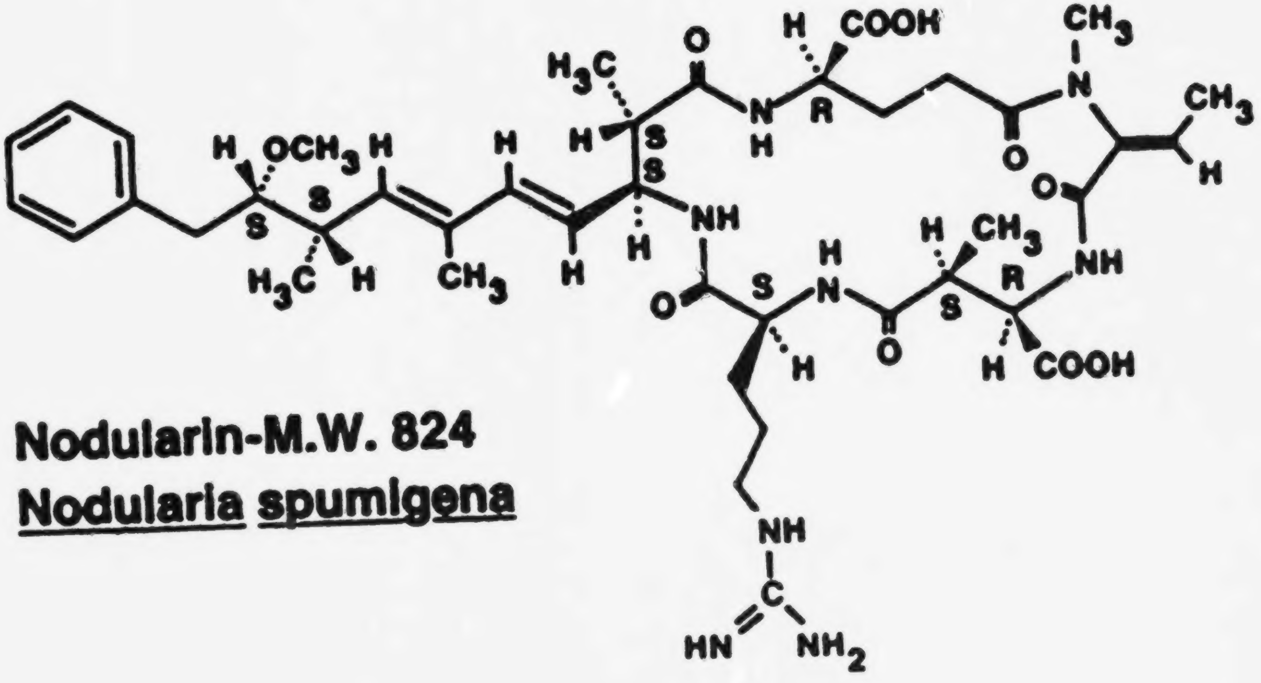

Nodularin-M.W. 824
Nodularia spumigena
H
OCH$_3$
S
H$_3$C
H
CH$_3$
COOH
NH
HN
NH$_2$
R
O

Figure 8. Structure of nodularin produced by the brackish water filamentous cyanobacterium *Nodularia spumigena*.

SOURCES OF MICROCYSTIN AND NODULARIN

Organism	Type of Microcystin
Microcystis aeruginosa	MCYST-LR, LA, YR, FR, YM, RR, LAba, AR, [DMAdda^5]MCYST-LR, [Dha^7]MCYST-LR, MCYST-M(O)R
Microcystis viridis	MCYST-RR, LR, YR, LA
Microcystis wesenbergii	MCYST-RR, LR (based upon mixed waterbloom samples)
Oscillatoria agardhii var. Isothrix	MCYST-RR [D-Asp^3]-MCYST-RR [D-Asp^{3,7}]-MCYST-RR
Oscillatoria agardhii var. (red pigmented)	MCYST-RR [D-Asp^7]-MCYST-RR
Anabaena flos-aquae	MCYST-LR [D-Asp^3]-MCYST-LR MCYST-HtyrR [D-Asp^3]-MCYST-HtyrR
Nostoc sp.	[ADMAdda^5]-MCYST-LR [ADMAdda^5]-MCYST-LHarg [D-Asp^3,ADMAdda^5]-MCYST-LR [D-Asp^3,ADMAdda^5]-MCYST-LHarg

Aphanizomenon and *Coelosphaerium* are reported to produce peptide hepatotoxins but specific ones have not been isolated.

Nodularia spumigena	Nodularin

Figure 9. Sources of microcystin (MCYST) and nodularin (NODLN). Nostoc toxins are reported by Sivonen et al. (1990b) and Namikoshi et al. (1990).

Table 2. Toxicity rating chart.[1]

Toxicity rating or class	Probable lethal oral dose for humans	
	Dosage[2]	*For Average Adult*
1. Practically nontoxic	> 15 g/kg	More than 1 quart
2. Slightly toxic	5-15 g/kg	Between pint and quart
3. Moderately toxic	0.5-5 g/kg	Between ounce and pint
4. Very toxic	50-500 mg/kg	Between teaspoonful and ounce
5. Extremely toxic	5-50 mg/kg	Between 7 drops and teaspoonful
6. Supertoxic	< 5 mg/kg	A taste (less than 7 drops)

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[1] Casarett and Doull's - Toxicology: The basic science of poisons. Third Edition. Macmillan Publishing Co. New York. 1986. p. 13.

[2] See Table 3.

Table 3. Comparison of toxicities of some biological toxins.

Toxin	*Source*	*Common Name*	*Lethal Dose*[1] (LD_{50})
BOTULINUM TOXIN-a	*Clostridium botulinum*	(BACTERIUM)	0.00003
TETANUS TOXIN	*Clostridium tetani*	(BACTERIUM)	0.0001
RICIN	*Ricinus communis*	(CASTOR BEAN PLANT)	0.02
DIPHTHERIA TOXIN	*Corynebacterium diphtheriae*	(BACTERIUM)	0.3
KOKOI TOXIN	*Phyllobates bicolor*	(POISON ARROW FROG)	2.7
TETRODOTOXIN	*Arothron meleagris*	(PUFFER FISH)	8
SAXITOXIN	*Aphanizomenon flos-aquae* and	(BLUE-GREEN ALGAE)	9
	Alexandrium sp.	(DINOFLAGELLATE ALGAE)	
COBRA TOXIN	*Naja naja*	(COBRA SNAKE)	20
NODULARIN	*Nodularia spumigena*	(BLUE-GREEN ALGAE)	50
MICROCYSTIN-LR	*Microcystin aeruginosa*	(BLUE-GREEN ALGAE)	50
ANATOXIN-a	*Anabaena flos-aquae*	(BLUE-GREEN ALGAE)	200
ANATOXIN-a(s)	*Anabaena flos-aquae*	(BLUE-GREEN ALGAE)	20
CURARE	*Chondrodendron tomentosum*	(BRAZILIAN POISON ARROW PLANT)	500
STRYCHNINE	*Strychnos nux-vomica*	(PLANT)	2000
AMATOXIN	*Amanita sp.*	(FUNGUS)	200-500
MUSCARIN	*Amanita muscaria*	(FUNGUS)	1100
PHALLOTOXIN	*Amanita sp.*	(FUNGUS)	1500-2000
SODIUM CYANIDE			10000

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[1] The acute LD_{50} in µg per kg bodyweight: intra-peritoneal injection: some with mice, some with rats

Table 4. Cases of animal poisonings (actual or suspected) caused by mass occurrences of cyanobacteria.*

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1878	L. Alexandrina; Australia	Sheep, horses, dogs, pigs	Stupor, unconsciousness,	*Nodularia spumigena*	Francis, 1878
1882-1884	Minnesota; USA	Cattle, horses, hogs	Rapid death (30 min or more)	*Gloeotrichia echinulata*	Porter, Arthur, Stalker ref. in Fitch et al., 1934
1900	Minnesota; USA	Several cattle	No description	*Aphanizomenon flos-aquae*	Nelson, ref. in Fitch et al., 1934; Olson, 1960
1917-1918	Alberta; Canada	Hogs, horses, cattle, poultry, wild birds	Hurried respiration, staggering gait, rigors	"Blue-green algae"	Gillman, 1925
1918	Minnesota; USA	1 sheep, 17 hogs and about 50 chickens	No pathological findings	*Coelosph. kuetzingianum* *Anabaena flos-aquae*	Fitch et al., 1934
1924	Ontaria; Canada	About 20 cattle	No description	*Anabaena*	Howard and Berry, 1933
1928	L. Vesijärvi; Finland	About 40 cattle	Rapid death (15 min or more)	*Anabaena lemmermannii*	Hindersson, 1933
1930	Minnesota; USA	9 cattle	Death after one and half h, no findings in autopsy	*Microcystis flos-aquae* *Microcystis aeruginosa*	Fitch et al., 1934
1933	Minnesota; USA	More than 21 sheep and chickens	Rapid death (minutes with guinea-pigs) no gross pathological findings	*Microcystis flos-aquae*	Fitch et al., 1934
1933	Minnesota; USA	45 turkeys, 4 ducks and 2 geese, 6 days later: cows pigs, horses and poultry	Rapid death (few minutes)	*Microcystis flos-aquae* *Anabaena flos-aquae* *Aphanizomenon flos-aquae*	Fitch et al., 1934
1933	Minnesota; USA	3 cattle	Rapid death, prostration convulsions	*Microcystis flos-aquae* *Anabaena flos-aquae*	Fitch et al., 1934
1934	L. Juksa; USSR	Number of cats	Paralysis of hind limbs, degeneration of liver	Blue-green algal bloom	Vinberg, 1954
1939	Colorado; USA	4 ducks, wild birds, carps, snakes, salamanders, a calf	Rapid death (minutes) no lesions	*Anabaena flos-aquae*	Deem and Thorp, 1939

Table 4. (continued)

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1913-1943	Free State and Transvall; S. Africa	Thousands of cattle, sheep and other animals	Liver damage, photosensitivity	*Microcystis toxica* (= *M. aeruginosa*)	Steyn, 1943, 1945
1943	Montana; USA	Sheep	Death after few hours	Algae	Quin, 1943
1944-1945	Iowa; USA	37 hogs, 4 sheep, 2 cattle, 3 horses and several dogs, cats, squirrels, chickens, turkeys and songbirds	Rapid death (4-12 min mice and guinea pigs)	*Anabaena flos-aquae*	Rose, 1953
1945	Manitoba; Canada	A horse, several calves two pigs and a cat	Muscular weakness paralysis	"Water bloom"	McLeod and Bondar, 1952
1946	North Dakota; USA	Cattle and deer	Hepatotoxicity + photosensitivity	"Water bloom"	Brandenburg and Shigley, 1947
1945	Bermuda	Cattle deaths	No description	*Aphanizomenon flos-aquae*	Prescott, 1948
1948	Iowa; USA	Few dogs	Distress, convulsions paralysis (death after 1 h 40 min, rabbit, oral)	*Anabaena flos-aquae*	Rose, 1953
1948	Minnesota; USA	Horses, a dog and wild birds	Typical algae poisoning	*Microcystis aeruginosa*	Olson, ref. in Scott, 1952
1948-1949	Ontario; Canada	Cattle deaths	Rapid death (minutes)	*Microcystis aeruginosa* *Anabaena* spp.	Stewart et al., 1950 MacKinnon, 1950
1950	Alberta; Canada	A cow, horses, pigs, dogs, turkeys, geese, chickens and wild birds	Partial paralysis, Liver mottled	*Microcystis*	O'Donoghue and Wilton, 1951
1949-1951	Manitoba; Canada	Heavy mortality of wild ducks	Rapid death (45 min)	*Aphanizomenon flos-aquae* *Microcystis aeruginosa*	Bossenmeyer et al., 1954
1951	Manitoba; Canada	A horse, 9 dogs	Muscular weakness paralysis, death within one hour	*Aph. flos-aquae* (99%) *A. flos-aquae* (0.9%) *M. aeruginosa* (0.1%)	McLeod & Bondar, 1952

Table 4. (Continued)

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1952	Iowa; USA	Thousands of Frankling's gulls, 560 ducks, 400 coots, 200 pheasants, 50 fox squirrels, 18 muskrats, 15 dogs, 4 cats, 2 hogs, 2 hawks, 1 skunk and 1 mink	Rapid death (minutes)	*Anabaena flos-aquae*	Firkins, 1953; Rose, 1953
1953	L. Semehovichi; USSR	Deaths of cats, dogs and water fowl	No description	*Microcystis aeruginosa*	Vinberg, 1954
1954	Saskatchewan; Canada	Pigs died, cattle unaffected	No description	*Anabaena flos-aquae*	Hammer, 1968
1956-	Texas; USA	Fish, frogs, chickens, ducks, turkey and cattle died or became ill	Death within 2 h enlarged liver (mice i.p.)	*Nostoc rivulare*	Davidson, 1959
1959	Alberta; Canada	14 beef cattle	Enlarged liver	"Blue-green algae"	MacDonald, 1960
1959	Saskatchewan; Canada	Approx. 30 dogs, 1 goose horses and cattle	Gastroenteritis with bowel haemorrhage, livers engorged and mottled	*M. aeruginosa/flos-aquae* *A. flos-aquae* *Aphanizomenon*	Senior, 1960; Dillenberg and Dehnel, 1960
1961	Saskatchewan; Canada	3 different lakes; 20 dogs; 3 cattle, perch; wild ducks	Mouse tests showed neurotoxicity in case of two lakes	*Anabaena flos-aquae*	Hammer, 1968
1962	Alberta; Canada	1 horse, 8 cows died, 60 cows were sick	No description	"Blue-green algae"	O'Donoghue, ref. in Gorham, 1964a
1962	Saskatchewan; Canada	3 dogs	No description	"Algae"	Hammer, 1968
1963	Rügen; GDR	About 400 ducks	Liver damage	*Nodularia spumigena*	Kalbe and Teiss, 1964
1964	Saskatchewan; Canada	5 dogs	Haemorrhagic enteritis	*Anabaena flos-aquae*	Hammer, 1968
1964	Saskatchewan; Canada	20 calves sick; 1 died	Haemorrhagic enteritis	*Anabaena, Aphanizomenon* *Nodularia*	Hammer, 1968
1964	New Hampshire; USA	Tons of fish died after $CuSO_4$ treatment	No description	*Aphanizomenon flos-aquae*	Sawyer et al., 1968

Table 4. (Continued)

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1965	New South Wales; Australia	20 lambs	Hepatocellular necrosis	*Anacystis cyanea* (= *M. aeruginosa*)	McBarron & May, 1966
1965	Saskatchewan; Canada	17 cattle	No description	*Anabaena flos-aquae* *Aphanizomenon* and *Microcystis aeruginosa*	Hammer, 1968
1966	New South Wales; Australia	16 sheep died and 50 were sick	Enlarged liver	*Anacystis cyanea* (= *M. aeruginosa*)	McBarron & May, 1966
?	Waipukurau; New Zealand	Lambs	Engorged, friable liver; haemorrhagic enteritis	*Microcystis aeruginosa*	Flint, 1966
1966	Saskatchewan; Canada	2 calves and 1 dog	Mouse test showed neurotoxicity	*Anabaena flos-aquae*	Hammer, 1968
1967	Saskatchewan; Canada	25 pigs	Vomiting, convulsions	*Anabaena*	Hammer, 1968
1971	New South Wales;	Deaths of honey bees	Rapid death (minutes with mice i.p.)	*Anabaena circinalis*	May & McBarron 1973
1972	Alberta; Canada	3 calves	Rapid death (8-15 min, mouse, i.p.)	*Anabaena flos-aquae*	Carmichael et al., 1977; Carmichael and Gorham, 1978
1972	Alberta; Canada	12-15 cattle	Hypersensitive to noise, staggering, weak, convulsions	*Anabaena flos-aquae*	Carmichael et al., 1977; Carmichael and Gorham, 1978
1973-1974	Hartbeespoort Dam; S. Africa	Cattle deaths	Microcystin poisoning	*Microcystis aeruginosa*	Toerien, et al., 1976
1974-1975	South Western and Western Australia	34 sheep, 52 lambs	Hepatic necrosis	*Nodularia spumigena*	Main et al., 1977
1975	New South Wales; Australia	20 lambs	Trembling, salivation, staggering leg weakness, collapse (liver changes with chickens, oral adm.)	*Anabaena circinalis*	McBarron et al., 1975

Table 4. (Continued)

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1975	Saskatchewan; Canada	34 cattle	Staggering, convulsions	*M. aeruginosa* (95%) *A. flos-aquae* (5%)	Carmichael et al., 1977; Carmichael and Gorham, 1978
1975	Danish Coast of the Baltic Sea	30 dogs were sick, 20 died	Hepatic necrosis	*Nodularia spumigena*	Lindstrøm, 1976
1976	Washington; USA	4 dogs died, 7 dogs, one horse and one cow were sick	Prostration, convulsion, respiratory failure (mice)	*Anabaena flos-aquae*	Soltero and Nichols, 1981
1977	Montana; USA	8 dogs and 30 cattle	Anatoxin-a poisoning	*Anabaena flos-aquae*	Juday et al., 1981
1977	Oklahoma; USA	Several cattle	Nausea, abdominal pain, diarrhea, muscular tremors, dyspnea, convulsions, death	*Microcystis* sp.	Zin and Edwards, 1979
1978	Rogaland; Norway	4 heifers	Microcystin poisoning	*Microcystis aeruginosa*	Skulberg, 1979
1978	Cheshire; England	3 cows	Acute haemorrhagic enteritis	*Oscillatoria agardhii*	Reynolds, 1980
1979	South Africa	3 rhinoceroses	Necrosis of the liver	*Microcystis aeruginosa*	Soll and Williams, 1985
1980	Vaal Dam; S. Africa	Cattle	Microcystis poisoning	*Microcystis aeruginosa*	Scott et al., 1981
1981	Illinois; USA	10 sows	Trembling, violent shaking, death with one-half hour	*Anabaena spiroides*	Beasley et al., 1983
1982	Swedish Coast of the Baltic Sea	9 dogs	Hepatic necrosis	*Nodularia spumigena*	Lind et al., 1983; Lundberg et al., 1983; Edler et al., 1985
1983	German Coast of the Baltic Sea	16 young cattle	Death 6-18 h, convulsions, haemorrhage in the cardiac region	*Nodularia spumigena*	Gussmann et al., 1985
1984	Finnish Coast of the Baltic Sea	1 dog and 3 puppies	Vomiting, weakness, liver damage	*Nodularia spumigena*	Persson et al., 1984

Table 4. (Continued)

Year	Location	Affected animals	Symptoms and findings	Organism	Reference
1984	Montana; USA	11 cattle	Rapid occurrence of death	*Anabaena flos-aquae* *Microcystis aeruginosa* *Aphanizomenon flos-aquae*	Spoerke and Rumack, 1985
1985	Alberta; Canada	Appr. 1000 bats, 24 mallards and American wigeons	Anatoxin-a shown in the green slime from carcasses	*Anabaena flos-aquae*	Pybus et al., 1986
1985	Wisconsin; USA	9 cows died, 11 were sick	Hepatotoxicosis	*Microcystis aeruginosa*	Galey et al., 1987
1985	South Dakota; USA	9 dogs	Anatoxin-a(s) poisoning	*Anabaena flos-aquae*	Mahmood et al., 1988
1985	Åland, Finland	Number of fish, birds and muskrat deaths	Liver fibrosis and gill damage (fish)	*Oscillatoria agardhii*	Eriksson et al., 1989
1986?	Alberta; Canada	16 cows	Anatoxin-a poisoning (possibly other amines present)	Not indicated	Smith & Lewis, 1987
1986	Illinois; USA	5 ducks; 13 pigs died	Anatoxin-a(s) poisoning	*Anabaena flos-aquae*	Cook et al., 1989
1987	Mississippi; USA	5 cows were sick	Staggering, salivation, muscle tremors, bloody diarrhea	*Microcystis aeruginosa*	Kerr et al., 1987
1988	Oklahoma; USA	4 cows, 6 calves, 18 pigs and 7 ducks died	Heapto- and neurotoxicosis	*Microcystis aeruginosa* *Anabaena flos-aquae*	Short & Edwards, 1990
1989	Rutland Water; United Kingdom	Deaths of 20 sheep and 14 dogs	Microcystin-LR poisoning	*Microcystis aeruginosa*	Report of The Natl. River Authorities United Kingdom - 1990
1989	Saskatchewan; Canada	16 cattle died	Neurotoxicosis	*Anabaena* sp.	Yong, et al., 1989
1990	Indiana; USA	2 dogs died	Anatoxin-a poisoning	*Anabaena flos-aquae*	Carmichael, 1991

* Updated from Sivonen, K. (1990) Ph.D. Thesis; University of Helsinki, Finland.

Table 5. Systematic surveys of the incidence of toxic waterblooms for a given geographic area has not been a regular part of the documentation for toxic cyanobacteria. It is difficult, and for the most part impractical, to sample all the water bodies in a geographical area for the presence of toxic cyanobacteria. Where systematic studies have been done, the percent incidence of waterbloom toxicity (number of sites with toxic waterblooms/number of sites with waterblooms sampled) has ranged from about 50-100. Areas where these studies have been conducted include: Minnesota (Olson 1960), Wisconsin (Repavich 1990), Alberta, Canada (Gorham 1962), Saskatchewan, Canada (Hammer 1968), Japan (Watanabe and Oishi 1980; Watanabe et al. 1988), German Democratic Republic (Henning and Kohl 1981), Netherlands (Leeuwangh et al. 1983), United Kingdom (Richard et al. 1983; Pearson 1990), Scandinavia (Berg et al. 1986), Sweden (Mattsson and Willén 1985), P.R. China (Carmichael et al. 1988), Greece (Lanaras et al. 1989), Finland (Sivonen et al. 1989, 1990a).

In assigning toxicity to a waterbloom which is a mixture of more than one cyanobacterial species or genus, it is often necessary to look at the level of toxicity in a chemical or biological assay and assign the toxic species responsible based on its dominance in the waterbloom sample. For example, if a waterbloom sample containing predominantly *Microcystis aeruginosa* has an LD_{50} intraperitoneal mouse of about 50 mg/kg with hepatotoxic signs of poisoning, it can be concluded that *M. aeruginosa* is most likely the toxic organism involved. If a waterbloom sample with an approximately 1:1 ratio of *Anabaena flos-aquae* and *Microcystis aeruginosa* has an LD_{50} intraperitoneal mouse of 100-200 mg/kg with neurotoxic signs of poisoning, it can be concluded that *Anabaena* is responsible for the toxicity observed, and the *Microcystis* component is not contributing to the toxicity observed. Not all cyanobacteria suspected of being toxic have been isolated and grown in the laboratory. Only species and strains within the genera *Anabaena, Aphanizomenon, Microcystis, Nodularia, Nostoc* and *Oscillatoria* have had toxins chemically identified. Work in this area is continuing in several laboratories around the world most notably in the United States. Based on the Report of the National Rivers Authority - United Kingdom (Pearson 1990), the cyanobacteria species listed in Table 6 are the confirmed toxic cyanobacteria species known.

FORMATION OF CYANOBACTERIA WATERBLOOMS AND SURFACE SCUMS

Multiple interacting physical, chemical, and biotic factors lead to the formation of cyanobacteria waterblooms (defined as the visible coloration of a water body due to the presence of suspended cells, filaments and/or colonies) and in some cases subsequent surface scums (surface accumulations of cells resembling clotted mats or paint-like slicks). Planktonic cyanobacteria are a natural component of the phytoplankton in most surface waters of the world. In northern latitudes like N. America and Europe waters supporting cyanobacteria growth have a sequence of algal dominance, generally being diatoms in the spring, then green algae followed by cyanobacteria in the summer and often into the autumn. It is generally agreed among aquatic microbiologists and limnologists who study waterbloom formation that 1) nutrient loading, 2) retention time of water within the water body, 3) stratification, and 4) temperature are the main factors influencing bloom formation and intensity.

Cyanobacteria owe their name of blue-green algae to the presence of accessary

Table 5. Case report: toxic cyanobacteria (blue-green algae)*

DATE	LOCATION	CYANOBACTERIA	TOXIN	COMMENTS	REFERENCES
Summer 1990	Pond near Huntington, Indiana	Anabaena flos-aquae	anatoxin-A	Neurotoxic poisoning of 2 family dogs	Hearld-Press of Huntington, Indiana - Sept. 30 and Oct. 1, 1990
Summer 1990	Clear Lake, California	Microcystis aeruginosa	microcystin	Toxicity based on bloom samples and drinking water samples. Assayed using ELISA antibody	California Dept. of Health, Sacramento
Summer 1989-90	Dahli Lake, near Manjouli, Inner Mongolia, P.R. China	Microcystis	hepatotoxin	Hepatotoxic poisoning of over 60 cattle - waterbloom not bioassayed	Personal Communication, Baolin Li, Director, Dahli Lake Fisheries Science Center (August 1991)
December 1989	American Lake near Tacoma, WA	Anabaena circinalas	anatoxin-A	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = 25 mg/kg	Tacoma-Pierce Co. Health Department, Tacoma, WA
September 1989	McDonald Lake, Colville Indian Reservation, Washington	Microcystis sp. and Aphanizomenon flos-aquae	microcystins	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 200 mg/kg	College of Pharmacy, Washington State University, Pullman
September 1989	Duley Lake, Colville Indian Reservation, Washington	Microcystis aeruginosa	microcystins	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 75 mg/kg	College of Pharmacy, Washington State University, Pullman

Table 5. (Continued)

DATE	LOCATION	CYANOBACTERIA	TOXIN	COMMENTS	REFERENCES
August 1989	Ft. Peck Lake, Montana	Anabaena sp.	microcystins	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 100 mg/kg	U.S. Army Corps of Engineers, Omaha District, Omaha, NE
June-Oct. 1989	Lake Okeechobee, Florida	Mixture of Anabaena sp. and Microcystis sp.	not identified	No hepatotoxins or neurotoxins - signs of poisoning indicated a contact irritant	South Florida Water Management, W. Palm Beach
October 1988	Charlie Lake, British Columbia	Microcystis aeruginosa	not identified	No hepatotoxins or neurotoxins signs of poisoning indicate contact irritant	Prov. of British Columbia; Ministry of Environment - Water Management
September 1988	Lake Istokpoga, Florida	Microcystis aeruginosa and Anabaena sp.	unidentified neurotoxin	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 300 mg/kg body weight	South Florida Water Management, W. Palm Beach
August 1987	Lake Okeechobee, Florida	Microcystis aeruginosa and Anabaena circinalis	microcystins	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 100 mg/kg body weight	South Florida Water Management, W. Palm Beach
July 1987	Superior, Nebraska	Anabaena flos-aquae	anatoxin-A(s)	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Animal Hospital, Superior, Nebraska

Table 5. (Continued)

DATE	LOCATION	CYANOBACTERIA	TOXIN	COMMENTS	REFERENCES
September 1986	Farm Pond near Griggsville, IL	Anabaena flos-aquae	anatoxin-A(s)	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Univ. of Illinois, College of Vet. Medicine, Urbana, IL. Cook, W.O. et al. 1989. Envir. Tox. Chem. 8: 915-922
August 1986	Farm Pond near Tolono, IL	Anabaena flos-aquae	anatoxin-A(s)	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Univ. of Illinois, College of Vet. Medicine, Urbana, IL. Cook, W.O. et al. 1989. Envir. Tox. Chem. 8: 915-922
October 1985	Lake Sissobogoma near Stone Lake, WI	Microcystis sp. and Anabaena sp.	hepatotoxin	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = 100 mg/kg	Cottage owner, Lake Sissobogoma, WI
September 1985	Farm Pond near Monroe, WI	Microcystis aeruginosa	microcystins	Signs of poisoning in lab mice and an Angus heifer indicated a hepatotoxin. LD50 intraperitoneal mouse = 10 mg/kg	F.D. Galey et al., J. of Vet. Res. 48(9): 1415-1420, 1987
September 1985	Lake Sakakawea, North Dakota	Microcystis aeruginosa plus Aphanizomenon flos-aquae	microcystins	Signs of poisoning in lab mice indicated a neurotoxin and a hepatotoxin. LD50 intraperitoneal mouse = approx. 100 mg/kg	U.S. Army Corps of Engineers, Lake Sakakawea Office, Riverdale, ND

Table 5. (Continued)

DATE	LOCATION	CYANOBACTERIA	TOXIN	COMMENTS	REFERENCES
August 1984	Canyon Ferry Reservoir, Montana	Aphanizomenon flos-aquae, Anabaena flos-aquae, and Microcystis aeruginosa	unidentified neurotoxin	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 100 mg/kg	Montana Dept. of Health Environmental Sciences
August 1983	Lake Erie at Toledo, Ohio	Microcystis aeruginosa	microcystins	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Univ. of Toledo, Dept. of Biology, Toledo, Ohio
September 1981	Pine Creek near Pinedale, WY	Anabaena sp. and Microcystis sp	neurotoxin	Field reports of dog poisoning indicated a neurotoxin. LD50 intraperitoneal mouse not determined	Vet. Services, Pinedale, WY
September 1981	Lake Lahonton, Nevada	Aphanizomenon flos-aquae	microcystins	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 180 mg/kg	Bioresources Center Desert Research Institute, Reno, Nevada
September 1981	Homer Lake near Urbana, IL	Microcystis aeruginosa	microcystins	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Univ. of Illinois College of Vet. Medicine, Urbana, Il.
July 1981	Harvey's Lake near Wilkesbarre, PA	Anabaenasp.	neurotoxin and hepatotoxin	Signs of poisoning in lab mice indicated a neurotoxin and a hepatotoxin. LD50 intraperitoneal mouse = approx. 100 mg/kg	Bureau of Water Quality Management, Wilkesbarre, PA

Table 5. (Continued)

DATE	LOCATION	CYANOBACTERIA	TOXIN	COMMENTS	REFERENCES
August 1980	Moore's Pond, Durham, NH	Aphanizomenon flos-aquae	saxitoxin and neosaxitoxin	Signs of poisoning similar to paralytic shellfish poisoning. LD50 intraperitoneal mouse = approx. 30 mg/kg	Dept. of Zoology, Univ. of New Hampshire, Durham, NH
July 1980	Pocono Highlands Lake, Pike Co., PA	Anabaena sp.	hepatotoxin	Signs of poisoning in lab mice indicated a hepatotoxin. LD50 intraperitoneal mouse = approx. 50 mg/kg	Bureau of Water Quality Management, Storoudsburg, PA
July 1980	Nelson Reservoir, Montana	Anabaena flos-aquae and Aphanizomenon flos-aquae	anatoxin A	Signs of poisoning in lab mice indicated a neurotoxin. LD50 intraperitoneal mouse = approx. 1500 mg/kg	Montana Dept. of Health Environmental Sciences
July-August 1977	Hebgen Lake, Montana	Anabaena flos-aquae, Microcystis aeruginosa and Aphanizomenon flos-aquae	anatoxin A and microcystins	Signs of poisoning in lab mice indicated a neurotoxin and a hepatotoxin. LD 50 intraperitoneal mouse = approx. 50 mg/kg	Gallatin Co. Health Dept., Bozeman, Montana

* Reported to or investigated by the author. Also see Table 4.

photosynthetic pigments called phycobilins. These pigments can make the cells and her the waterblooms and surface scums blue-green to brownish-red. These accessory pigme allow cyanobacteria to utilize low light intensities by absorbing light over a wide-band of t visible spectrum. Thus cyanobacteria can grow at lower depths and overall lower lig intensities.

There is a reasonable consensus in the literature that water temperatures below 20 are unfavorable for the mass development of the common waterbloom forming gene *Anabaena, Aphanizomenon* and *Microcystis* (Paerl 1987). Slower growth rates at low temperatures mean that longer water retention times are required for cyanobacteria achieve substantial increases in population. Even under optimal growth rates, determin by laboratory studies, doubling rates of some nuisance cyanobacteria are similar to oth phytoplankton such as green algae and diatoms (Table 7). This means that waterbloo and surface scums are more common to lakes, ponds and reservoirs where retention tim are longer than in rivers where dilution rates tend to be higher.

Waterblooms of cyanobacteria are often observed in water bodies undergoing increase nutrient enrichment especially those water bodies whose nutrient status can be classed either eutrophic to hypereutrophic (hypereutrophy is defined as the condition where nutrie inputs exceed the nutrient demands of phytoplankton). There are three soluble inorgan nutrient species considered to be of major concern with respect to phytoplankton growt including the cyanobacteria. These include nitrate-nitrite (NO_3/NO_2), ammoni (NH_3/NH_4^+) and orthophosphate (PO_4^{-3}) (Paerl 1987). While the requirements for thes nutrients by cyanobacteria are not necessarily greater than other phytoplankto cyanobacteria appear to employ other factors to assist them in becoming dominant persisting in the water body. These involve 1) the ability to store phosphorus within the ce making them capable of cell division when phosphorus becomes limiting, and 2) fixation atmospheric nitrogen by several of the toxic bloom forming filamentous cyanobacteri especially *Anabaena, Aphanizomen, Nodularia* and *Nostoc*. If other nitrogen sources ar depleted, these cyanobacteria have an advantage over other planktonic algae and ca dominate for long periods. *Microcystis* and *Oscillatoria*, which do not fix nitrogen, requi eutrophic to hypereutrophic conditions regarding nitrogen to become dominant. It has bee popular to describe ratios of the availabilities of nitrogen (N) to phosphorus (P) which mig favor cyanobacteria growth over other phytoplankton. It has been shown that a lower rat of N:P favors cyanobacteria (10 to 16 N:1 P) over most other algae (16 to 23 N:1 P). The ratios only apply when these nutrients are in limited supply. Under limited nutrie conditions phosphate is considered to be the best predictor of cyanobacterial abundanc Most waterblooms that cause acutely lethal poisonings occur when conditions of eutrop to hypereutrophy prevail; thus N:P ratios are of minimal use in predicting presence potentially toxic bloom situations (Pearson 1990).

Other factors that influence cyanobacterial dominance in waterblooms concern the consumption by aquatic invertebrates and their ability to regulate cellular buoyancy. Whi many planktonic algae are a major food source for microcrustaceans (i.e. *Daphnia* copepods and protozoa, the cyanobacteria are not extensively eaten (Hanazato and Yasu 1987; Hanazato 1991). There are several exceptions to this trend of cyanobacteria bein

Table 6. Freshwater blue-green algae in blooms implicated in poisoning incidents: confirmed toxic blue-green species and purified toxins.

Species	As Bloom Components	As pure cultures Cells	 Purified toxin
Anabaena circinalis	+	+	+
Anabaena flos-aquae	+	+	+
Anabaena lemmermanii	+	nd	na
Anabaena solitaria	+	nd	na
Anabaena spiroides	+	nd	na
Anabaena venenosa	+	nd	na
Anabaenopsis milleri	+	nd	+
Aphanizomenon flos-aquae	+	+	+
Coelosphaerium kutzingianum	+	nd	na
Cylindrospermopsis raciborskii	+	+	na
Cylindrospermum sp.	+	+	+
Gloeotrichia ecinulata	+	+	na
Gloeotrichia pisum	+	nd	na
Gomphosphaeria lacustris	+	nd	na
Gomphosphaeria naegeliana	+	nd	na
Microcystis aeruginosa	+	+	+
Microcystis incerta	+	nd	na
Microcystis viridis	+	+	+
Microcystis wesenbergii	+	nd	na
Nostoc sp.	+	+	+
Oscillatoria agardhii	+	+	+
Oscillatoria agardhii var. isothrix	+	+	+
Oscillatoria rubescens	+	nd	na
Oscillatoria sp.	+	nd	na
Synechocystis sp.	+	nd	na

+ = toxic in mouse bioassay
nd = not determined
na = not available

From: Report of The National Rivers Authority. 1990. United Kingdom.

Table 7. Laboratory-determined optimal growth rates of a variety of nuisance blue-green algal species as well as diatom and chlorophycean species. Included are data from species isolated from the Neuse River (Paerl 1987) as well as selected (cited) studies

Species	Doublings/day	Citation
Microcystis aeruginosa (blue-green alga)	0.75-1.20	(Paerl 1987)
Aphanizomenon flos-aquae (blue-green alga)	0.85-1.50	(Paerl 1987)
Anabaena flos-aquae (blue-green alga) Lake Windermere	1.13	(Foy et al. 1976)
Anabaena flos-aquae (blue-green alga) Lake Windermere	0.96	(Fay & Kulasooriya 1973)
Oscillatoria agardhii (blue-green alga)	1.25	(van Liere 1979)
Scenedesmus spp. (chlorophycean)	0.55-0.75	(Paerl 1987)
Chlorella spp. (chlorophycean)	0.50-0.85	(Paerl 1987)
Cyclotella meneghiniana (diatom)	0.65-0.95	(Paerl 1987)

poor food sources. A number of flagellates, amoebae and ciliates can act as predators on cyanobacteria (Dryden and Wright 1987). Studies on Lake Kasumigaura, Japan have shown that the rotatorian *Philodina erythrophthalma* and the oligochaete *Aeolosoma hemplichi* can degrade *Microcystis* blooms (Inamori et al. 1987, 1988). In addition, the ciliate *Nassula* has also been shown to be a voracious consumer of planktonic cyanobacteria especially toxigenic *Oscillatoria, Aphanizomenon* and *Anabaena* (Canter et al. 1990). It has also been observed that *A. hemplichi* and *P. erythrophthalma* can dominate even in the presence of toxic *Microcystis*. This observation is being exploited in Japan where those invertebrates are used on "biofilms" to remove cyanobacteria and their toxins in water treatment processes (Sudo and Aiba 1984; Inamori et al. 1987, 1988). This reduced grazing by aquatic invertebrates gives the planktonic cyanobacteria another advantage in their competition with other phytoplankton. Indeed the production of toxins by cyanobacteria, to inhibit grazing pressures by zooplankton, may be one of the main ecological roles for these compounds. Studies have shown that cyanobacteria may be inhibitory or toxic to diatoms (Keating 1978), zooplankton (Stangenberg 1968; Porter and Orcutt 1980; Snell 1980; Lampert 1981; Infante and Abella 1985; Nizan et al. 1986; Fulton and Paerl 1987) and crustaceans (Lightner 1978; Gentile and Maloney 1969; Sasner and Ikawa 1980).

More recently Demott et al. (1991) have shown acute lethality in four species of zooplankton to the heptapeptide microcystin-LR and the pentapeptide nodularin. Survivorship of the zooplankters in the presence of toxic *Microcystis* cells was strongly influenced by the ability of different zooplankters to discriminate toxic cells from nontoxic cells (i.e. the green alga *Chlamydomonas*). The authors concluded that zooplankton have evolved both physiological and behavioral adaptations which enhance their abilities to coexist with toxic cyanobacteria. This would suggest that toxicity of cyanobacteria is a common phenomena and occurs at all times (or much more often than revealed by animal poisonings). Acute lethal or chronic exposure by mammals is largely a phenomena of heavy waterbloom and surface scum occurrences.

Heavy waterbloom formation leading to surface scums of cyanobacteria is a consequence of the buoyancy regulating behavior of the common planktonic cyanobacteria. Of the main toxic genera only *Oscillatoria* does not regulate its buoyancy. Buoyancy regulation is an active process in cyanobacteria. Cell inclusions called gas vesicles inflate and deflate in an effort to regulate the cell at an optimum depth for nutrient and light availability. Cells receiving too little light become more buoyant and float upwards. When too much light is received by the cells, buoyancy is lost allowing the cells to sink. Gases for buoyancy regulation by these gas vesicles comes from photosynthesis. Therefore, carbon availability (expressed as dissolved inorganic carbon) in the form of CO_2, HCO_3 (bicarbonate) and CO_3 (carbonate) is important not only for photosynthesis but for buoyancy regulation as well.

Buoyancy regulation by planktonic cyanobacteria is influenced greatly by the mixing of waters within a water body. Energy input from the sun warms water near the surface so that it tends to float (stratify) on top of the deeper colder water. If wind energy is not great enough to mix the water, this thermal stratification can last for a few hours, days or for much of the summer. Stratification tends to induce rapid dominance by buoyant populations of cyanobacteria if conditions of nutrient availability also exist. Thus the low wind days of summer and fall lead to unhindered thermal stratification and buoyancy regulation. As biomass of the cyanobacteria increases, the light penetration will decrease. This forces the cyanobacteria population to increase their buoyancy moving closer to the surface. Even if wind action mixes the population of cells, light penetration is reduced by the biomass present, and the cells continue to increase their buoyancy. At night the cells have no reference point for light with which to decrease their buoyancy and eventually the cells are "overbuoyant" and form surface scums. These surface scums tend to clump together due to the gelatinous nature of material surrounding the cells and filaments. As long as the low wind pattern persists the scum becomes thicker and thicker. Gentle wind and wave action aids in scum formation and will carry the cells inshore especially on the lee side of a water body. Thus scums can appear literally overnight and can persist for as long as wind and wave action do not redisperse the cells throughout the mixing zone. These surface scums inshore represent the greatest threat to animals including humans. Humans, however, are naturally "averse" to these surface scums (both their visual appearance and their smell) and do not willingly make contact with the potentially toxic cells. Even if wind action is able to move the scum away from the shoreline, the strength of the wind may not be enough to mix the cells back into the water. Under these conditions mats of scums can be moved about a water body as rafts of cells. This phenomenon is not common but has been observed in Hartbeespoort Dam, a massively hypereutrophic reservoir in South Africa (Zohary and Roberts 1990; Zohary et al. 1990). If these scums are not remixed, the cells become stressed releasing their contents including toxins into the water. When the scums pile up on filters of a water treatment facility, high levels of toxins can be released into the water distribution system for consumption by humans (Berg et al. 1987).

Once a population of cyanobacteria such as *Microcystis* is established in a water body it continues to create waterblooms and scums on a yearly basis. Reynolds et al. (1981) has described such a cycle for the toxigenic genus *Microcystis*. In the winter, vegetative cells of *Microcystis* survive on the surface layers of the sediments. In the spring to early summer a short series of cell divisions leads to cell clusters that begin to develop gas vesicles and thus buoyancy regulation is established. As nutrient and temperature conditions, continue to improve, growth is increased and waterblooms can form. Throughout this period the action of nutrient availability, buoyancy regulation, overbuoyancy conditions and stratification determine the extent and duration of waterblooms and surface scums. As winter approaches gas vesicle collapse occurs and rates of sedimentation exceed those of cell positive buoyancy.

CONTROL OF CYANOBACTERIA POPULATIONS

Waterblooms of cyanobacteria are a natural occurrence in many freshwater bodies. The natural aging process leading to eutrophication, followed by waterblooms and surface scums is a common phenomena in many lakes not subject to cultural eutrophication. The main problem with cyanobacteria waterblooms and their toxins arises in those cases where natural or cultural eutrophication leads to the presence of waterblooms and/or scums in recreational waters or those waters used as a drinking water supply. Thus the need to eliminate or control waterblooms will be greatest for reservoirs, lakes and rivers with high human and/or animal use value. In many cases elimination of cyanobacterial populations once they have established themselves in a water body is neither practical nor appropriate.

Factors important to the occurrence of cyanobacterial blooms include 1) nutrient input, 2) water retention time, 3) grazing pressure, 4) buoyancy regulation and 5) stratification. Of these, nutrient deprivation has the highest probability of providing long term control benefits for cyanobacteria. It is also one of the most expensive. In a study on the Neuse River, North Carolina, Paerl (1987) recommended that a 30-40% reduction in spring loading of NO_3^- had the best chance of minimizing *Microcystis aeruginosa* as a competitive and ultimately dominant phytoplankter. In North America some emphasis has also been placed on reducing phosphates discharged to sewage treatment plants by reducing the use of polyphosphate-based detergents. It has been pointed out, however, that these detergent based phosphates account for only 25% of the load to sewage treatment plants and that the bulk of phosphates is derived from human wastes. As a result emphasis in Europe has been on phosphate stripping as a means of controlling phosphorus and thus waterblooms. In any attempt at nutrient input control, consideration must also be given to the internal loading of nutrients. Years of nutrient buildup in the sediments particularly phosphorus means that some consideration needs to be given to removal of sediments, a procedure whose ease depends on the size and depth of a water body. Controlling factors such as physical (reducing light, destratification and scum corrals), biological (planktivorous organisms) and chemical (algicides) might prove useful in managing cyanobacteria waterblooms. While light removal is an obvious way to eliminate photosynthetic cyanobacteria from a water body, it is seldom practical to cover a water body unless it is confined and well defined such as some constructed reservoirs (Sykora et al. 1980). Destratification of a water body, provided it is deep enough to become thermally-stratified, can be an effective control of waterblooms and surface scums. Permanent destratification will depress growth of buoyant cyanobacteria but only where mixed depths exceed, by about a factor of two, the depth of water through which light penetrates (Pearson 1990).

Biological control of cyanobacteria populations can involve the use of planktivorous fish, planktonic zooplankton, cyanobacteria lysing bacteria and cyanophages. Planktivorous fish are sometimes used to control cyanobacteria populations, or more often control is achieved along with the raising of these fish for food. The author's experience over the past several years in China has found that high rates of clearance and thus control of cyanobacteria is achieved by the use of Silver Carp (*Hypophthalmichthys molitrix*), Grass Carp (*Ctenopharyngodon idellus*), Bighead Carp (*Aristichthys nobilis*) and Telapia (*Telapia nilotica* and *T. mossambica*). In fish ponds and even lakes of significant size, these fish easily remove the larger colonies of *Microcystis* and in the process leave smaller unicellular and flagellated species which are a better food source for zooplankton. The author has also noted that the *Microcystis* blooms fed upon by these planktivorous fish are toxin producers. The fish appear not to be affected by consumption of the toxic algae. In fact the author has observed fecal pellets composed entirely of *Microcystis* colonies, from these fish, floating on the surface of fish ponds in several areas of China. When collected and bioassayed these pellets are found to contain high levels of microcystin hepatotoxins. Based on these observations it would be worthwhile to investigate use of these fish for the control of toxic cyanobacteria. The introduction and use of exotic species of planktivorous fish to control toxic cyanobacteria waterblooms would of course require careful consideration of the environmental effects these introductions might make. It can be noted, however, that Grass Carp are already being used in the United States to control macrophyte growths (Leslie et al. 1987) and *Telapia* is being raised in Canadian farm dugouts as a summer "put and take" form of fish farming (H. Peterson, Saskatchewan Research Council - personal communication).

The use of zooplankton or cyanophages has not received as much attention as planktivorous fish. Occasionally cyanobacteria populations have been observed to collapse as a result of grazing by the ciliate *Nassula* (Canter et al. 1990). In addition, the Japanese are using a rotatoria and oligochaete to control waterblooms of toxic *Microcystis*. Conversely, there is also good evidence showing that toxic *Microcystis, Nodularia* and *Anabaena* have very detrimental effects on the crustacean *Daphnia* and the copepod *Diaptomus* (Demott et al. 1991).

Microbiological control of cyanobacteria populations using bacteria or cyanophages has been advocated for some time (Safferman and Morris 1964, 1979; Burnham and Fraleigh 1983). These studies tend to show that it is difficult to maintain stocks of the lytic organisms for ready application to a waterbloom and the lysing organism's host may be too specific to control a random bloom of toxic cyanobacteria. However, there is some merit to further study of these forms of cyanobacteria population control.

In some instances it may be desirable to remove the surface scum of cyanobacteria or to prevent it from coming inshore by the use of floating booms. This limits animals and humans from having direct access to high concentrations of cells and toxins. This has been used at times on small farm ponds to prevent livestock from watering in a surface scum (Carmichael and Schwartz 1984). The use of booms, such as used to collect oil slicks, are also being tested in areas of Europe. The booms are used to corral the surface scum so that it can be pumped off the surface and removed from the lake (Pearson 1990). Obviously timing is important in using these booms, as surface scums are often dispersed within minutes. There also needs to be careful disposal of the collected scum especially if it is toxic.

Another potential, although not often recommended, method to control cyanobacteria populations is the use of chemicals. While there are several compounds that will kill algae, there are few which are specific to algae or to cyanobacteria. The short term solution to cyanobacteria in fresh water is to add copper, usually as copper sulfate, to the lake, reservoir or farm pond. This is done by towing sacks of copper sulfate round a lake by boat, or spreading copper sulfate from aircraft. The costs of this treatment are considerable, as it needs to be repeated each time the cyanobacteria begin to bloom. Some water supplies may have to be treated several times during a single summer. Copper is used in the water to kill the cyanobacteria. The consequence of this cell death is the release of cell contents, including toxins if present, into the water. For this reason, copper sulfate is best applied as the bloom is forming. This minimizes the taste, odor and toxicity that are released into the water. If an alternative water source is available, the treated water supply should be disconnected for 5-7 days to allow the copper content of the water to drop and taste and odor from the cyanobacteria to decrease. As would be expected, small farm ponds and dugouts are easier to control than larger lakes and reservoirs. It is also generally impractical (and ecologically unsound) to use copper in flowing water bodies such as rivers or streams. Use of algicides in many states of the United States as well as in other countries may be regulated by the Department of Natural or Environmental Resources, or other regulatory agencies, and an algicide permit may be required. Copper sulfate ($CuSO_4$) can be purchased in granular or block form (sometimes called bluestone). When $CuSO_4$ ($CuSO_4 \cdot 5 H_2O$) is used, the recommended concentration is from 0.2 to 0.4 ppm with an upper limit of 1 ppm (mg/l). This is equivalent to: (a) 4 to 8 lb per million gallons of water (upper limit 20 lb), (b) 0.65 to 1.3 ounces per 10,000 gallons of water, (c) 1.4 to 2.8 lb per acre-foot of water or (d) 20 to 40 g per 50,000 liters of water (Beasley et al. 1983).

Livestock should not be watered from copper-treated water sources for at least five days after the last visible evidence of a surface bloom. However, there is no way to guarantee the absence of toxins in the water even after this time. Since sheep are particularly susceptible to copper poisoning, they should not be allowed access to treated water until the copper has sedimented out. Other algicides are available, for example quinones and other organic herbicides (Fitzgerald et al. 1952). They are not widely used and in some countries are prohibited from use in water. However, development and approval of organic algicides may become necessary if copper resistance by the cyanobacteria develops requiring alternate chemical controls.

HEALTH EFFECTS OF CYANOBACTERIA

Since most of the waterbloom and surface scum forming cyanobacteria are capable of producing toxins, their presence in a water body used for recreational or drinking water purposes should be of concern to animal and human health.

Hazards to Wild and Domestic Animals

The most life-threatening situation occurs when overbuoyant cells form surface scums and accumulate along a shoreline in calm or low wind weather conditions. The accumulation of these scums along shorelines or in bays presents watering animals with potentially lethal concentrations of cells and toxins. Published reports of animal deaths from cyanobacteria blooms extend back more than a century (Francis 1878). These reports have documented losses of cattle, sheep, pigs, horses, ducks, geese, and chickens. Wild animal poisonings from cyanobacteria include amphibians, snakes, water fowl, rodents, bats, bees, zebras and rhinoceros (Table 4). In many of these older reports of animal deaths the conclusion that cyanobacteria toxins were responsible rests on the presence of a waterbloom along with the observation that animals were watering from the bloom followed by illness or death. The more recent reports include collection of bloom material and verification of the bloom's toxicity followed by isolation and characterization of the toxin.

Two groups of animals, aquatic invertebrates and fish, do not show the same susceptibility to the cyanotoxins as do mammals and birds. Fish kills, occurring during periods of heavy cyanobacteria blooms, have happened although there is not a lot of direct evidence to show that fish are widely susceptible to the toxins. Some cases do exist, for example, fish killed in blooms of hepatotoxic *Oscillatoria* in Scandinavia showed liver damage consistent with the effects of microcystins. Intraperitoneal injections of microcystins into rainbow trout (Phillips et al. 1985), the common carp (*Cyprinus carpio*) (Eriksson et al. 1986), and anatoxin-a injection (oral and intraperitoneal) into goldfish (Carmichael 1974) resulted in mortalities with the same signs of poisoning as in mammals. As stated earlier in this report, the planktoniverous fish such as silver carp, grass carp, bighead and telapia appear resistant to the microcystins. It is not known whether this resistance is related to lack of absorption, detoxification or lack of toxin receptors by this group of fish. It may explain, however, some of the variability observed with fish deaths by cyanobacteria, and it also points up the possible use of these fish as biological control agents for cyanobacterial populations.

Toxicity variation in zooplankton may in part be explained by the recent work of Demott et al. (1991). They found that survivorship of the microcrustacean *Daphnia* and the copepod *Diaptomus* to toxic *Microcystis* cells or purified toxin was strongly influenced by both physiological sensitivity and feeding behavior. Relatively good survivorship by *Daphnia pulicaria* was associated with low sensitivity to purified toxin and rapid feeding inhibition in the presence of toxic cells. In contrast, poor survivorship by *Daphnia pulex* was associated with greater physiological sensitivity and low inhibition of feeding on toxic cells. Intermediate survivorship by the copepod *Diaptomus birgei* was associated with food selection capabilities coupled with physiological sensitivity and uninhibited feeding on toxic cells. The results suggest that zooplankton have evolved physiological and behavioral adaptations which enhance their abilities to coexist with toxic cyanobacteria. These new laboratory experimental results may explain some of the previous observations obtained on aquatic microorganisms.

Toxicity in zooplankton is not always associated with mouse toxicity from the hepato- or neurotoxins (Mills and Wyatt 1974; Nizan et al. 1986). The rotifer *Branchionus calyciflorus* can maintain high populations during blooms of hepatotoxic *M. aeruginosa* (Fulton and Paerl 1987) or neurotoxic *An. flos-aquae* (Starkweather 1981). Maloney and Carnes (1966) did not find any effects of a hepatotoxic bloom of *M. aeruginosa* on fish, microcrustaceans or diatoms. It is possible that aquatic microorganisms and aquatic invertebrates, as well as fish, have evolved physiological and behavioral adaptations which allow them to coexist with toxic cyanobacteria. It does appear that these adaptations could be stressed and break down when heavy waterblooms and scums of toxic cyanobacteria are present in a water supply. Under these conditions, species with low adaptations to the toxins or toxic cells could be reduced or eliminated, shortening food chains and upsetting the ecological balance of a natural water body. As already mentioned, the primary types of toxicosis that pertain to wild and domestic animal poisonings are acute hepatotoxicosis and peracute neurotoxicosis. Most poisoning by cyanobacteria involves hepatotoxicosis caused by the structurally similar group of small molecular weight cyclic peptides called microcystin or nodularin (Figures 5, 6, 8).

Of the peptide toxin producing genera, *Microcystis* is the main worldwide offender, and of the three toxic species identified to date, i.e. *M. aeruginosa*, *M. viridis* and *M. wesenbergii*, only *M. aeruginosa* has been used in clinical hepatotoxicosis studies. Animals affected by the hepatotoxins may display weakness, reluctance to move about, anorexia, pallor of the extremities and mucous membranes, and at times mental derangement. Since all animals in a herd, group or flock often drink from the same water supply, most or all of them will be affected within a similar time period. Death occurs within a few hours to a few days and is often preceded by coma, muscle tremors and general distress (Galey et al. 1987). It is generally agreed at this time that death results from intrahepatic hemorrhage and hypovolemic shock (Falconer et al. 1981; 1988; Theiss et al. 1988).

Upon necropsy, animals show hepatic enlargement (increases in liver weight of 2-3x are common) and often intrahepatic hemorrhage. Hepatic necrosis begins in the centrilobular region and proceeds periportally. Hepatocytes are initially rounded and dissociated, later they are necrotic. With time course studies in laboratory animals, dissociated hepatocytes can appear in the central veins and eventually pass into the pulmonary vasculature (Theiss et al. 1988; Hooser et al. 1989). Ultrastructurally, in the rat and mouse model, intact cells retain their nuclei and mitochondria although these organelles are swollen. Rough endoplasmic reticulum becomes vesiculated and degranulated (partial or total loss of ribosomes from the vesicles) (Dabholkar and Carmichael 1987).

Animals, especially cattle, that survive an acute cyanobacterial hepatotoxicosis may experience photosensitization. This photosensitization may be so severe that cows refuse to nurse their calves (Stowe et al. 1981; Carmichael and Schwartz 1984).

In general, therapies for algal toxicosis in livestock have not been investigated in detail. The most likely beneficial agents are powdered charcoal (Stowe et al. 1981) and cholestyramine (Questran, Mead Johnson, Evansville, IN) (Dahlem et al. 1988). Although the cholestyramine is more effective, activated charcoal is more readily available and less expensive. Therapeutic support measures in poisoned animals might also include administration of whole blood and glucose solutions (Beasley et al. 1989). Certain chemicals have also been used experimentally to prevent microcystin hepatotoxicity in laboratory animals. These include cyclosporin-A (Hermanskey et al. 1990a, 1991), rifampin (Hermanskey et al. 1990b, 1991), and silymarin (Merish et al. 1991). These antagonists have been most successful when given prior to or coadministered with the toxin. At present it is not known how these antagonists might be affecting microcystin toxicity, but it is thought to involve inhibition of toxin uptake by the hepatocyte.

A summary of field and laboratory studies involving wild and domestic animal hepatotoxicosis is given in Table 8.

The final type of cyanobacterial animal toxicosis to be considered concerns neurotoxicosis due to the alkaloid anatoxins and aphantoxins. Cyanobacterial neurotoxicosis results from ingestion of toxic *Anabaena flos-aquae, An. spiroides, Aphanizomenon flos-aquae, and Oscillatoria* (Carmichael 1988; Sivonen et al. 1989a). Although these genera may also produce peptide hepatotoxins together with the neurotoxins, the neurotoxins are more rapidly acting, and therefore, dominate the field and clinical syndromes.

Produced by strains of *Anabaena* and *Oscillatoria*, the alkaloid neurotoxin antx-a (Figure 1) is a potent postsynaptic depolarizing neuromuscular blocking agent (Carmichael et al. 1979). This toxin causes death within minutes to a few hours depending on the species, the amount of toxin ingested, and the amount of food in the stomach (Carmichael 1988). Clinical signs of antx-a poisoning follow a progression of muscle fasciculation, decreased

Table 8. Animal hepatotoxicosis by cyanobacterial toxins.

Animal	Clinical signs and lesions	References
Cattle, sheep	hepatotoxicosis - clinical signs: recumbancy/weakness, diarrhea, tachypnea/dyspnea, trembling, photosensitization, aberrant behavior, ataxia, pale mucous membranes, algae on skin/ hair, weight loss, tachycardia, anorexia. Lesions include: liver-enlarged, congested, mottled or friable; enteritis/hemorrhage, edema, anemia, algae in digestive tract, diffuse centrilobular hepatocyte degeneration.	Steyn (1945); Dillenberg and Dehnel (1960); Senior (1960); Konst et al. (1965); Main (1977); Skulberg (1979); Reynolds (1980); Stowe et al. (1981); Jackson et al. (1984); Kerr et al. (1987); Galey et al. (1987)
Dogs	hepatotoxicosis - clinical signs: abdominal discomfort, recumbancy, diarrhea, vomiting, secretions from the eyes and mouth, anorexia, ataxia, coma. Lesions include: swelling/ mottling of the liver, hemorrhagic enteritis, pulmonary edema, algae in the intestine.	Senior (1960); Dillenberg and Dehnel (1960); Edler et al. (1985)
Birds (turkeys, ducks, geese)	hepatotoxicosis - clinical signs: restlessness, eye blinking, defecation, clonic spasms. Lesions include: hepatic enlargement/ hemorrhage, pulmonary edema, enteritis; algae in digestive tract.	Steyn (1945); Brandenberg and Shigley (1947); Dillenberg and Dehnel (1960); Konst et al. (1965); Jackson et al. (1986)
Fish (rainbow trout)	hepatotoxicosis - clinical signs: nontoxic when fish were immersed in a culture of *M. aeruginosa*; died following i.p. administration with hepatic necrosis.	Phillips et al. (1985)
Monkey (vervet)	hepatotoxicosis - clinical signs: no prodromal signs from oral dosing before death. Lesions include: liver necrosis and hemorrhage.	Tustin et al. (1973)
Rhinoceros	hepatotoxicosis - lesions include: hepatic enlargement, hemorrhage and necrosis.	Soll and Williams (1985)

movement, abdominal breathing, cyanosis, convulsions and death. In addition, opisthotonos (rigid "s" shaped neck) is observed in avian species. In smaller laboratory animals death is often preceded by leaping movements, while in field cases larger animals collapse and sudden death is observed (Smith et al. 1987). No known therapy exists for antx-a, although respiratory support may allow sufficient time for detoxification to occur followed by recovery of respiratory control (Valentine, personal communication).

More recent neurotoxicosis involving cyanobacteria have become associated with a potent cholinesterase inhibitor termed anatoxin-a(s) (Figure 1) (s = salivation factor). Antx-a(s) is a guanidinium methyl phosphate ester (M/Z 252) (Matsunaga et al. 1989). To our knowledge this represents the first example of a naturally occurring organophosphate anticholinesterase. Antx-a(s) is very toxic (i.p. mouse $LD_{50} \approx 20\ \mu g/kg$) but is somewhat unstable and becomes inactivated with elevated temperatures (> 40°C) and under alkaline conditions. Toxicosis associated with antx-a(s) has been observed in the field (Mahmood et al. 1988; Cook et al. 1989).

Clinical signs of antx-a(s) toxicosis in pigs include hypersalivation, mucoid nasal discharge, tremors and fasciculation, ataxia, diarrhea, and recumbency. In ducks the same symptoms occur plus regurgitation of algae, dilation of cutaneous vessels in the webbed feet, wing and leg paresis, opisthotonos, and clonic seizures prior to death (Cook et al. 1989). Laboratory rodents appear tolerant of antx-a(s) when dosed intragastrically but susceptible by the intraperitoneal route (Cook et al. 1988). Clinical signs in mice include lacrimation, viscous mucoid hypersalivation, urination, defecation, and death from respiratory arrest. Rats exhibit the same clinical signs plus chromodacryorrhea (red-pigmented "bloody" tears). At the LD_{50}, survival times are 5-30 minutes (Mahmood and Carmichael 1987; Cook et al. 1988).

Therapy for antx-a(s) toxicosis has not been investigated thoroughly. Mahmood and Carmichael (1986b) found that atropine would antagonize the muscarinic effects of anatoxin-a(s), but at the dose given animals still died. Because antx-a(s) does not appear to cross the blood-brain barrier, it may be possible to use a cholinergic blocker such as methyl atropine nitrate (Metropine-Pennwalt, Rochester, NY) or glycopyrrolate (Robinul-V, AH Robbins Co., Richmond, VA) (Beasley et al. 1989). Hyde and Carmichael (1991) found that *in vivo* pretreatment with physostigmine and high concentrations of 2-PAM were the only effective antagonists against a lethal dose of anatoxin-a(s).

Some strains of *Aph. flos-aquae*, so far found only in the state of New Hampshire, produce the potent paralytic shellfish poisons (PSP) saxitoxin and neosaxitoxin (referred to as Aphantoxin II and I respectively) (Mahmood and Carmichael 1986a) (Figure 1). These sodium channel blocking agents inhibit transmission of nervous impulses and lead to death by respiratory arrest. For such toxicosis, therapy is best approached by trying to limit further absorption from the gastrointestinal tract by using activated charcoal, and a saline cathartic plus artificial respiration when needed.

Hazards to Human Health

Cyanobacteria cause health risks not only to wild and domestic animals but also to humans (MacKenthan et al. 1964; Schwimmer and Schwimmer 1964, 1968; Bourke and Hawes 1983; Stein and Borden 1984; Carmichael et al. 1985; Gorham and Carmichael 1988; Codd and Poon 1988; Falconer 1989). Reports over the past 60 years have provided case reports on the adverse effects of cyanobacteria in freshwater to human health. These reports come from the USA, India, Canada, Zimbabwe, Norway, the Baltic coast, USSR, Australia, and the U.K. In almost all cases little or no attempt was made to critically evaluate the reports and carry out proper epidemiological studies. In addition, none of the reports document human deaths. This probably has a lot to do with the lack of follow-up studies by public health officials. The reports that have occurred can be divided into those involving allergic reactions and skin irritations and those where gastroenteritis and hepatoenteritis are the result of ingestion of cyanobacteria. Infrequent, but recurrent, cases involve swimming, bathing or showering in water containing a cyanobacteria waterbloom. Symptoms include allergic reactions, asthma, eye irritation, rashes and blistering around the mouth and nose (Heise 1949, 1951; Cohen and Rief 1953; Mittal et al. 1979; Graves and Arnold 1961). These reports came from Brazil, China, Europe, Norway, USA, and the UK. All other etiological agents such as bacteria, fungi or protozoa were ruled out as probable causes of the symptoms.

The earliest public health report implicating cyanobacteria in gastroenteritis afflicting a population drawing water from a common source occurred on the Ohio River in 1931. Low rainfall caused stagnation of flow and cyanobacterial accumulation in a side branch of the river used as a water source. When rain caused water to move from the affected side branch to the main river, reports of gastroenteritis were reported in towns downstream from the side branch. The toxin(s) responsible for the illnesses were not identified, nor were the species of cyanobacteria (Tisdale 1931; Veldee 1931). More recently in Sewickley, Pennsylvania, a widespread outbreak of gastroenteritis was attributed to the cyanobacterium *Schizothrix calcicola* which occurred in that city's uncovered water supply (Lippy and Erb 1976; Sykora et al. 1980). Toxin or toxins produced by this filamentous cyanobacterium was the apparent cause of an illness that struck about 62% of the population served by the Sewickley water utility. Characteristics of the outbreak included diarrhea, abdominal cramps and other gastrointestinal type symptoms. No definitive toxin was identified as the causative agent. It was suggested by subsequent laboratory studies with *S. calcicola*, that lipopolysaccharide endotoxins could have caused the gastrointestinal problems (Keleti et al. 1979, 1981). However, it is also possible that had the cyanobacterial cyanotoxins, i.e. microcystins, been tested for, they may also have been found to be present. While no confirmed toxic cyanobacteria was found to be responsible for the outbreak, the reservoir was covered (preventing growth of the photosynthetic cyanobacteria) and no further outbreaks have occurred.

An abundant organism in water supply reservoirs, *Microcystis aeruginosa*, has been implicated in repeated outbreaks of seasonal gastroenteritis among children in Salisbury, Rhodesia (now called Harare, Zimbabwe). Several supply reservoirs provided water to different regions of the city, but only the reservoir containing blooms of *Microcystis* supplied water to the affected population. The gastroenteritis occurred when the bloom naturally lysed at the end of summer (Zilberg 1966). Since microcystins are normally confined within the cyanobacterial cells, and do not enter the water until lysis or cell death, the relationship between the age and condition of a bloom and the public health consequences is particularly important. Water treatment by flocculation and sedimentation, together with sand filtration, will remove live cyanobacterial cells and debris, but not toxins in solution.

In a retrospective epidemiological study undertaken in Australia, the effects of a *Microcystis* bloom on a public drinking water supply were investigated. The bloom had been carefully studied as part of an ongoing survey of toxic cyanobacteria in water supplies, so that the dates when the bloom developed, its toxicity and the time when the water supply authority lysed the bloom with 1 ppm copper sulfate were accurately known. Liver function data for all patients tested in the surrounding region during the time prior to the bloom, while the bloom was occurring including its treatment phase, and after the bloom, were analyzed by computer. Measurements of liver enzyme concentrations in human serum were sorted by date of sample and geographical location of the patient's home. A statistically significant increase in gamma glutamyl transferase (GGT), indicative of toxic injury to the liver, occurred only in the population supplied by the affected reservoir, and only at the time of the bloom (Falconer et al. 1983). There was no evidence of infectious hepatitis affecting this population, or of alcoholic festivity at the time.

A severe outbreak of hepatoenteritis requiring hospital treatment of over 140 individuals, was also attributed to toxic cyanobacteria present in an Australian water supply. In this case, severe injury was caused to a large number of children, requiring intravenous fluid replacement for up to two weeks before recovery. In this instance only individuals drinking reticulated water from a single dam were affected, and the clinical cases began a few days after a heavy cyanobacterial bloom on the reservoir was lysed by the addition of copper sulfate (Bourke et al. 1983). Cyanobacteria cultured from this reservoir were later identified as *Cylindrospermopsis raciborskii*, and their toxicity assessed. The dry cells had an LD_{50} of 64 mg/kg by intraperitoneal (i.p.) injection in mice. Unlike *Microcystis* or *Anabaena* toxins, which kill within 15-60 minutes of i.p. injection of a lethal dose, mice given this material had an average survival time of 19 hours. Histopathological changes included massive hepatocyte necrosis, plus necrotic tissue injury to lungs, kidneys, adrenals and intestine (Hawkins et al. 1985). *C. raciborskii* is a tropical species, and the island on which the outbreak occurred is located off the Queensland coast of Australia. Nothing is known of the chemistry of the toxin involved. Cyanobacteria produce detectable endotoxins of the lipopolysaccharide type which may have implications for public health, especially in infants and the sick (Keleti 1979). However, their low oral toxicity indicates they are unlikely to cause major problems in normal drinking water (Keleti et al. 1981). As contaminants of dialysis fluids they may be pyrogenic (Hindeman et al. 1975). They also cause turbidity in soft drinks prepared from water containing cyanobacteria.

In general, it has been found that the cyanotoxins are not removed by conventional water treatment procedures of coagulation-sedimentation-rapid sand filtration-chlorination (Wheeler et al. 1942; Hoffman 1976; Falconer et al. 1983, 1989; Keijolu et al. 1988; Himberg 1989). These same groups have found that active carbon treatment is effective if properly used. In addition, ozonization (Keijola et al. 1988; Himberg et al. 1989) effectively eliminated toxicity, probably by a cleavage of the double bond of the ADDA component of microcystin.

Diarrhea associated with a cyanobacteria-like organism --- a new cyanobacterial health threat?

Most reports of gastroenteritis and diarrhea associated with cyanobacteria waterblooms are from known members of the planktonic cyanobacteria. In recent years there have been several outbreaks of diarrhea accompanied by anorexia, fatigue and myalgia involving > 100 patients in Southeast Asia and the U.S. (Long et al. 1990). In all cases the causative agent has been a cyanobacterium-like organism (CLO) which has not been identified (Long et al. 1991). If the agent is found to be a cyanobacterium, it will be the first proven case of a cyanobacteria capable of infecting and persisting in the human intestinal tract. At this time it is not known whether the CLO produces any type of toxin.

Carcinogenic, teratogenic and tumor promotion studies in the laboratory: Implications for long term effects on humans.

In agricultural regions, or heavily populated areas, there may be continuous water blooms of toxic cyanobacteria in drinking water reservoirs. While water supply authorities often control these blooms, the conventional method of copper sulfate treatment lyses the organisms, releasing toxic cell contents into the water. It is therefore important to evaluate any long-term public health consequences of chronic ingestion of low concentrations of the lysed organisms.

The chronic administration of *Microcystis* extract at low concentration in the drinking water of mice resulted in increased mortality, particularly in male mice, together with chronic active liver injury. The deaths were largely due to endemic broncho-pneumonia, indicating an impairment of disease resistance. Only 6 tumors were seen in the 430 mice killed at intervals up to 57 weeks of age. However, four of the six tumors were in females ingesting the highest *Microcystis* concentration (Falconer et al. 1988). This result led to an investigation of the tumor-promoting activity of orally administered *Microcystis* in mice to which dimethylbenzanthracene had been applied to the skin. Results of these trials showed that there were significant increases in the growth of skin papillomas in mice given *Microcystis* but not *Anabaena* to drink (Falconer and Buckley 1989; Falconer 1991).

The finding that microcystin activated phosphorylase a (Runnegar et al. 1987) has led to some studies which show that microcystin-LR, YR, RR and nodularin are potent inhibitors of protein phosphatases type 1 (PP1) and type 2A (PP2A) (Adamson et al. 1989; Honkanen et al. 1990; MacKintosh et al. 1990; Matsushima et al. 1990; Yoshizawa et al. 1990). This finding is important since inhibition of PP indicates that microcystins are tumor promoters.

Because microcystins are preferentially taken up by hepatocytes, it is expected that the main health threat as a tumor promoter would be in liver tumor promotion. Nishiwaki-Matsushima et al. (1992), working at the National Cancer Institute in Tokyo, Japan, has just completed a two stage tumor promotion study which demonstrates tumor formation in rat liver by microcystin-LR. These types of experiments clearly indicate that microcystins are a health threat in drinking water supplies.

The threat from microcystins as liver tumor promoters in humans is given further support from a report recently published by Yu (1989). The report states that in China primary liver cancers (PLC) rank third for men and fourth for women in the overall cause of cancers. The report also states in several areas of China the rates of PLC do not correlate with PLC causing agents such as aflatoxin and hepatitis B virus. Instead, for the high rate regions most people drank pond and ditch water, while in low-rate regions, even within the same county or only a street apart within the same village the people drank water either from wells or a river. Further long term epidemiological studies continued to show that people who drank pond and ditch water had a higher risk of PLC than people who drank well water. The association between use of stagnant surface drinking water and liver cancer was noticed in the counties of Qidong, Haimin, and Nanhui. After 1973 the inhabitants of Qidong County were encouraged to dig wells and give up drinking pond and ditch water. As a result, by 1979 the rate of PLC had stabilized for the County. In neighboring areas of the county where ditch and pond water continued to be used for drinking water, the PLC rates were continuing to increase.

These studies did not address the question of whether the ditch and pond waters contained cyanobacteria or the liver tumor promoting microcystins. However, the author's work over the past 5 years in collaboration with the Hydrobiological Institute in Wuhan, Hubei, P.R. China clearly show that a very high number (> 80%) of all ponds sampled throughout southern, central and northeast China had high cyanobacterial populations during the summer and fall periods. In addition, most of these populations were *Microcystis aeruginosa* and, of the *Microcystis* samples tested, 100% produced moderate to high levels of the liver tumor promoting cyclic peptide microcystins (Carmichael et al. 1988a,b; Zhang et al. 1991; Carmichael et al., unpublished data). It is expected that further studies will be done on the question of drinking water sources, PLC and microcystins in these and other areas of China.

The marine cyanobacterium, *Lyngbya majuscula*, causes skin irritation on contact and contains the well characterized tumor-promoting toxins, lyngbyatoxin A (Fujiki et al. 1984) and aplysiatoxins (Fujiki et al. 1985). These marine blue-green toxins have only been tested by skin application so that little is known about their oral toxicity. Other cyanobacterial species that cause skin irritations occur in both marine and fresh waters. Epidemiological and experimental research is therefore needed on possible tumor promotion in human populations by cyanobacterial extracts in water supplies. Until now, however, no studies have demonstrated cancer initiation by cyanobacterial extracts or toxins.

Teratogenic activity from chronic oral administration of *Microcystis* extracts has been demonstrated in mice. Animals of both sexes were provided with a water supply containing *Microcystis* extract for 17 weeks prior to mating. This was continued through pregnancy up to day 5 of lactation. Autopsy of the neonates showed approximately 10% of the otherwise normal neonatal mice had small brains, exhibited by a gap between the brain and the skull. Of three such brains subjected to serial sectioning, hippocampal neuronal damage was evident in one (Falconer et al. 1988).

In summary, whether the tumor-promoting effects or the teratogenic activity of cyanobacteria are of public health significance awaits suitable human epidemiological analysis of cancer deaths and birth defect frequency in populations exposed to this risk.

SUMMARY

An important function of this status report is to provide an analysis of the role that waterbodies which contain high amounts of cyanobacterial cells and toxins might play in the health of animals and humans. Clearly, cyanobacterial planktonic populations have been a part of the ecology of waterbodies throughout geological time. It is conceivable that the evolution of secondary metabolites such as the microcystins andanatoxins have occurred along with other adaptations which have conferred competitive advantages for the planktonic cyanobacteria.

Nutrient enrichment (eutrophication) is also a natural event in waterbodies as they age. However, human activities have increased the nutrient aging processes of lakes, ponds and rivers at a rapid rate and on a global scale. Where once a lake or pond might experience seasonal cycles of phytoplankton that might not have the cyanobacteria dominate for more than a few weeks a year, these same waterbodies today have nutrient levels such that blooms of planktonic cyanobacteria occur earlier in the year, persist longer and produce higher biomasses (including surface scums) than would have occurred even a few years ago. Man-made reservoirs are particularly subject to the eutrophication process because they have fewer of the physical and biological characteristics which natural lakes do, and because they are often situated closer to sources of human activity (agricultural, recreational or municipal) which contribute more to the process of eutrophication.

Not enough research has been done on the factors which lead to the formation of toxic waterblooms of cyanobacteria. Whereas it was once thought that there were distinctly toxic and nontoxic waterblooms, the development and use of more sensitive assay methods such as ELISA (Chu et al. 1989, 1990; Chu and Carmichael, unpublished data) have shown that samples testing negative by the mouse bioassay still contain levels of microcystins in the μg/g (dry weight cells) range. This lends support to the argument that all the major planktonic cyanobacteria, i.e., *Anabaena, Aphanizomenon, Microcystis, Nodularia* and *Oscillatoria* produce cyclic peptide hepatotoxins, and production occurs at all or most phases of the growth cycle. The factors which result in high levels of toxin, i.e. $\geq$ 1 mg/g dry weight cells, should be investigated, since it is these levels which allow enough toxin to be ingested by watering animals to cause acute lethality.

Many officials remain unconvinced of the need to monitor or regulate cyanobacteria toxins in municipal or recreational water supplies. The skepticism seems to arise from the fact that, despite the presence of cyanobacteria toxins in many bodies of water, there are no confirmed cases of human death or illness from cyanobacteria toxicosis. Several reasons, which probably act in combination, may explain the lack of reported human toxicity. First, vectors which concentrate toxins the way shellfish concentrate marine paralytic shellfish toxins are uncommon in freshwater. Where they do exist, as in Europe or Scandinavia, people tend not to eat freshwater shellfish, except locally. Second, while the cyanotoxins are very toxic, and therefore, require only a low concentration to induce lethal toxicity, they also have a steep dose-response curve. Specifically, animals must ingest a lethal or nearly lethal dose before observable signs of poisoning appear. Such high concentrations of toxin occur only when waterblooms form surface scums. While surface scums are certainly the most dangerous situation for watering animals, humans tend to avoid them because of their sight and smell. Third, because of better water quality management and cooler winters, water supplies in North America and Europe don't support high concentrations of toxic cyanobacteria year round. When waterblooms occur in drinking water supplies, filtration and dilution reduce levels in the finished water below those that cause acute toxicosis. Without sensitive detection methods and an understanding of the possible low-dose chronic health effects in humans, there is a reluctance by public health officials to pursue cyanobacterial toxins as agents of water-based disease.

Current levels of understanding about the widespread occurrence of toxic cyanobacteria coupled with more sensitive methods of detection, especially immunoassay, plus the new evidence showing that the major group of cyanotoxins, the cyclic peptide hepatotoxins, are potent liver tumor promoters, argues for a prompt reversal of the present lack of effort on cyanotoxins and water-based disease.

RECOMMENDATIONS FOR RESEARCH AND DEVELOPMENT

1) Continue efforts to develop predictive models to quantify the formation of cyanobacterial blooms. These models should be developed with thought toward their use as models to devise management plans for various water bodies.

2) Further research to develop measures to control eutrophication and minimize development of cyanobacteria waterblooms and scums. These can include: effects of land use practices and nutrient run-off; nutrient traps and nutrient stripping methods and monitoring programs to define the occurrence and distribution of toxic cyanobacteria.

3) Support development of sensitive, rapid and accurate methods for the detection of cyanotoxins. A likely method for immediate development is the use of ELISA antibodies for the major group of cyanotoxins -- the cyclic peptide liver tumor promoting microcystins and nodularin.

4) Support efforts to adopt an existing method or develop a standard procedure for analytical analysis and purification. This would in turn support efforts to make toxin standards available for research.

5) Support research leading to an understanding of the transport, fate and ecological role the cyanotoxins have in aquatic environments.

6) The prokaryotic cyanobacteria can be genetically manipulated and studied with many of the same techniques available to study molecular and cellular genetics of other prokaryotes. Therefore support should be given to the study of the physiological and genetic mechanisms involved in toxin production.

7) Support studies on the taxonomy and classification of cyanobacteria. This information is critical to effective communication about toxic cyanobacteria and their toxins.

8) Finally, it is recommended that administrative support be developed within the USEPA to carry out several aspects of the work on cyanobacterial toxins. These include:

   a) educating and advising Federal, State and local public health workers, and the general public on toxic cyanobacteria;

   b) linking with appropriate authorities in other parts of the world so that information can be exchanged and collaborative research projects can be developed and supported; and

   c) developing certain USEPA "in house" research projects on some aspects of cyanobacteria and their toxins.

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APPENDIX

THE DIRECTORY TO TOXIC BLUE-GREEN ALGAE (CYANOBACTERIA) LITERATURE

THE DIRECTORY TO
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